



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

Primary Hyperoxaluria Type 1

Rare Genetic Disorder of Increased Endogenous Oxalate Synthesis

Primary Hyperoxaluria Type 1 (PH1):

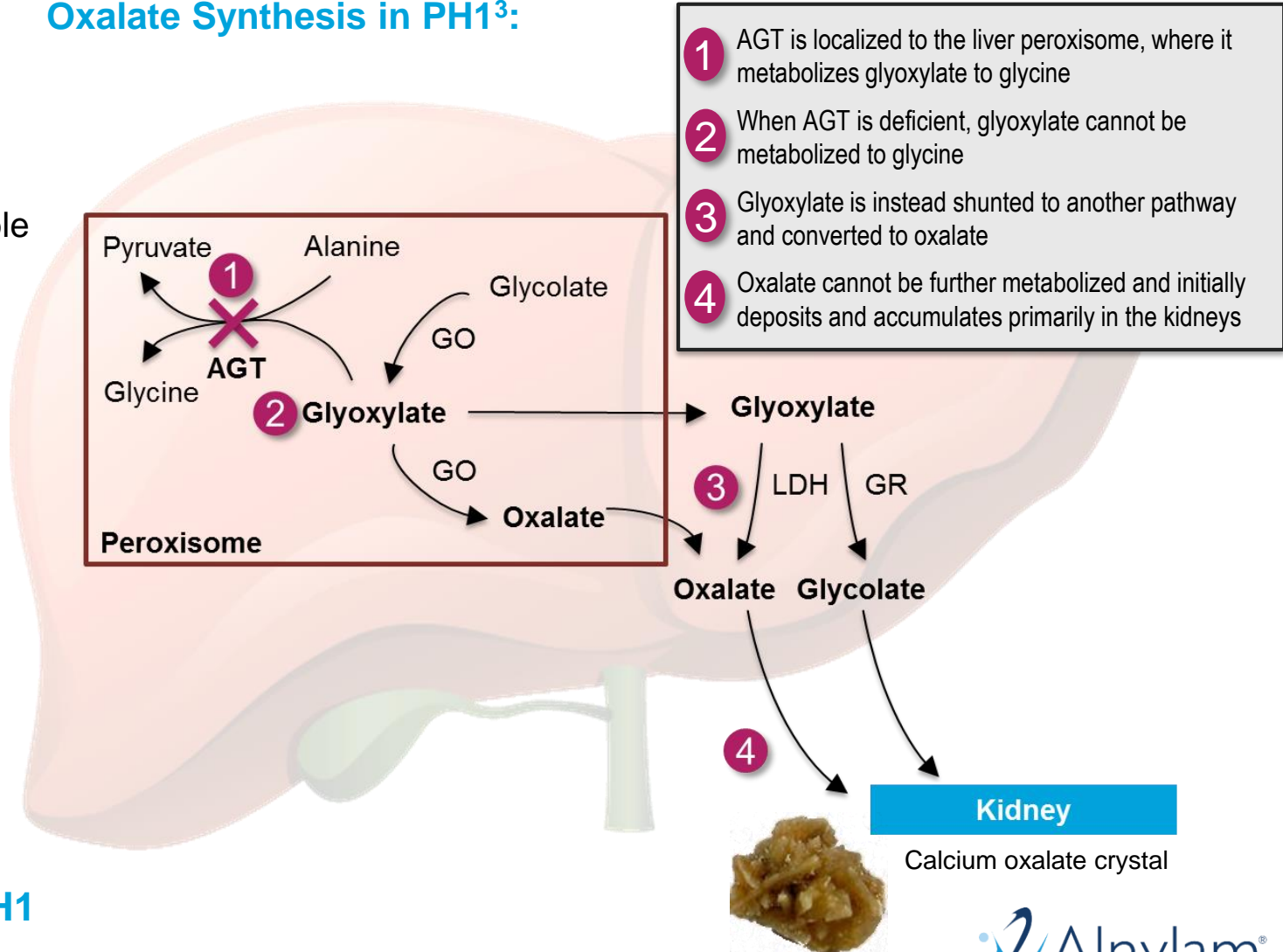
- Due to defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- Phenotype varies significantly in patients and may present at any age, typically in childhood, with variable rates of progression
- Prevalence of PH1: 1-3/1,000,000 in Europe¹ and ~ 32/1,000,000 in Middle East²

Pathophysiology¹:

- Overproduction of oxalate results in highly insoluble calcium oxalate crystals
- Precipitation of calcium oxalate crystals leads to urolithiasis, nephrocalcinosis, and kidney failure
- Disease course ultimately leads to multi-organ damage from systemic oxalosis, affecting bones, eyes, blood vessels, heart, thyroid, skin, and other tissues

No therapies are approved for treatment of PH1

Oxalate Synthesis in PH1³:



- 1 AGT is localized to the liver peroxisome, where it metabolizes glyoxylate to glycine
- 2 When AGT is deficient, glyoxylate cannot be metabolized to glycine
- 3 Glyoxylate is instead shunted to another pathway and converted to oxalate
- 4 Oxalate cannot be further metabolized and initially deposits and accumulates primarily in the kidneys

Lumasiran

Investigational RNAi Therapeutic for Primary Hyperoxaluria Type 1

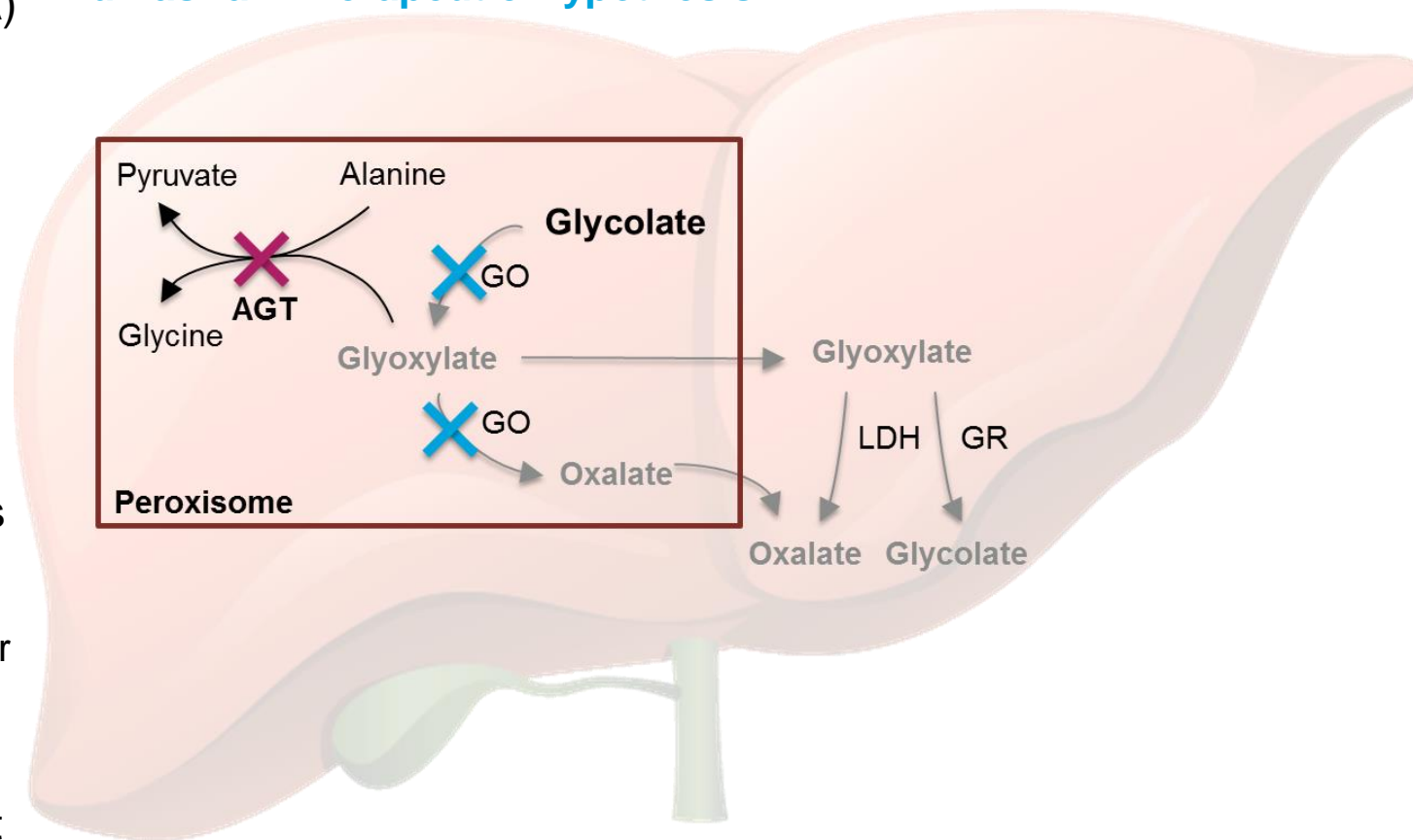
Lumasiran (ALN-GO1):

- SC-administered small interfering RNA (siRNA)
 - Harnesses natural RNA interference (RNAi) mechanism
 - Specifically designed for targeted liver delivery—site of oxalate synthesis

Therapeutic Hypothesis:

- Lumasiran targets liver *hydroxyacid oxidase 1 (HAO1)* mRNA, decreasing production of glycolate oxidase (GO) and hence reduces hepatic oxalate production
- Glycolate is soluble, excreted renally and does not precipitate in the kidney
 - Lack of clinical effect from elevated glycolate is highlighted in several reported cases of known or suspected GO inactivity¹⁻⁴
- In preclinical animal models as well as healthy volunteers receiving lumasiran in Phase 1/2 (Part A), increased levels of glycolate were not associated with any safety findings⁵⁻⁶

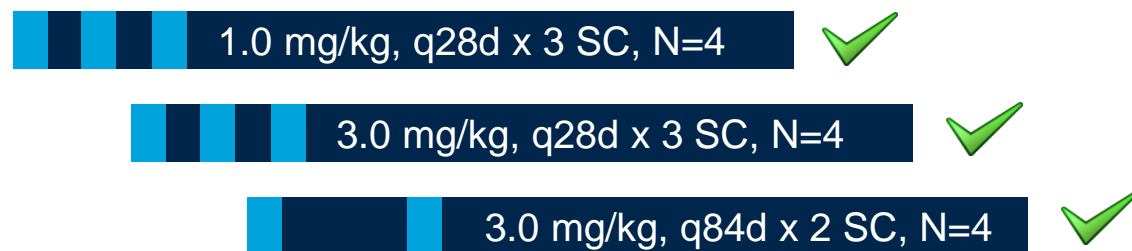
Lumasiran Therapeutic Hypothesis:



Lumasiran Phase 1/2 Study*

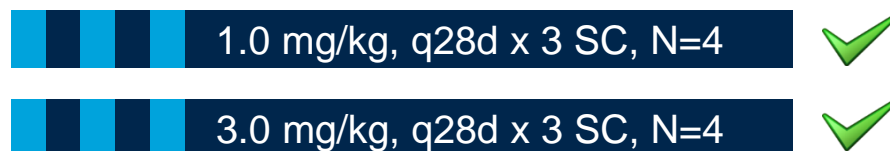
Study Design† & Demographics: Part B (Patients with PH1)

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



Patients randomized to placebo received subsequent dosing of lumasiran

Expansion Cohorts | Open-label



✓ Dosing Complete

Inclusion Criteria:

- Patients with PH1
- Ages 6-64 years
- eGFR > 45 ml/min/1.73m²
- Urinary oxalate excretion ≥ 0.70 mmol/24h/1.73m²

Key Endpoints:

- Safety and tolerability
- Urinary oxalate excretion
- Urinary oxalate to creatinine ratio

*Data cut-off: 15 Aug 2018

†NCT02706886; EudraCT Number: 2015-004407-23

PH1, primary hyperoxaluria type 1; eGFR, estimated glomerular filtration rate

Lumasiran Phase 1/2 Study*

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

| Baseline Characteristics | 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 (42.4 –130.7) |
| Mean Urine Oxalate Content, mmol/24hr/1.73m ² (range) | 1.69 (0.83–2.97) |
| Mean 24-hour Urine Oxalate:Creatinine Ratio (range) | 0.17 (0.07–0.30) |
| Mean Plasma Glycolate, µmol/L (range) | 193.83 (18.0–491.0) |

Patients have been on study for a median of 7 months (range: 5-14) since first dose

- Patients are actively transitioning to continue lumasiran dosing in the open-label extension[†] study once follow-up completed for Part B

*Data cut-off: 15 Aug 2018

[†]NCT03350451; EudraCT Number: 2016-003134-24

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

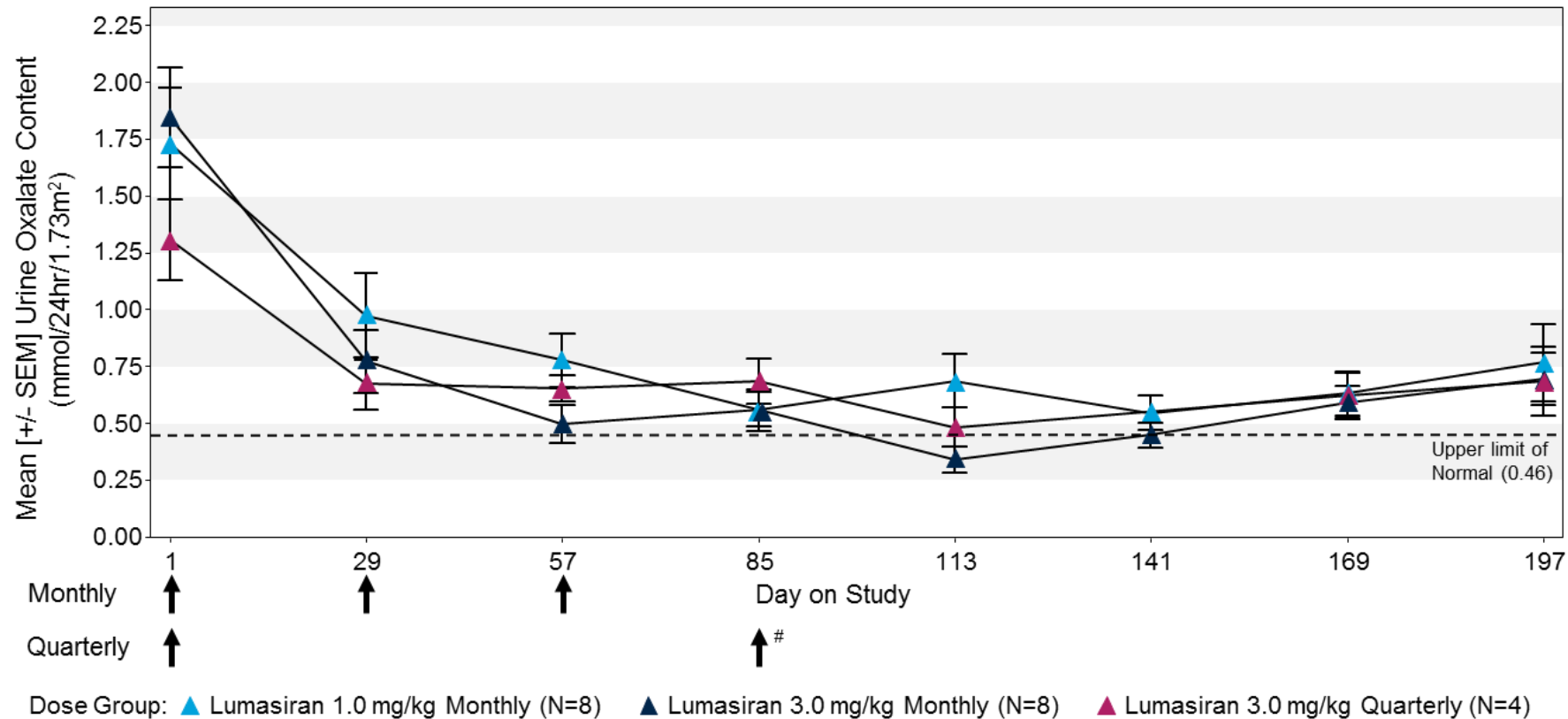
- No discontinuations from study treatment
- SAEs reported in 1 (33%) patient during placebo dosing and 5 (25%) patients after lumasiran dosing; none related to study drug
 - Placebo: 1 patient with SAE of acute pyelonephritis and kidney stones
 - Lumasiran: 2 patients with kidney stones; 1 patient with vomiting; 1 patient with gastroenteritis; and 1 patient with abdominal pain, fever, and vomiting
- AEs reported in 3 (100%) patients during placebo dosing and 19 (95%) patients after lumasiran dosing
 - Majority of AEs were mild or moderate in severity and unrelated to study drug
 - Severe AEs reported 1 (33%) patient during placebo dosing (acute pyelonephritis) and 2 (10%) patients after lumasiran dosing (1 patient with acute renal colic and kidney stone, and 1 patient with kidney stone); none related to study drug
 - AEs reported in >3 pts among patients receiving lumasiran: vomiting, pyrexia, cough (N=6 each); abdominal pain, headache (N=5 each); and rhinitis (N=4)
 - Self-limiting injection site reactions (ISRs) reported in 3 (15%) patients receiving lumasiran; all mild or moderate
- No clinically significant laboratory changes

Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Urinary Oxalate Content in Part B (Patients with PH1)

Mean maximal reduction in urinary oxalate of 75% (range: 43-87%) relative to baseline after lumasiran dosing in all cohorts† (N=20)

- 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

Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Urinary Oxalate Reduction in Part B (Patients with PH1)

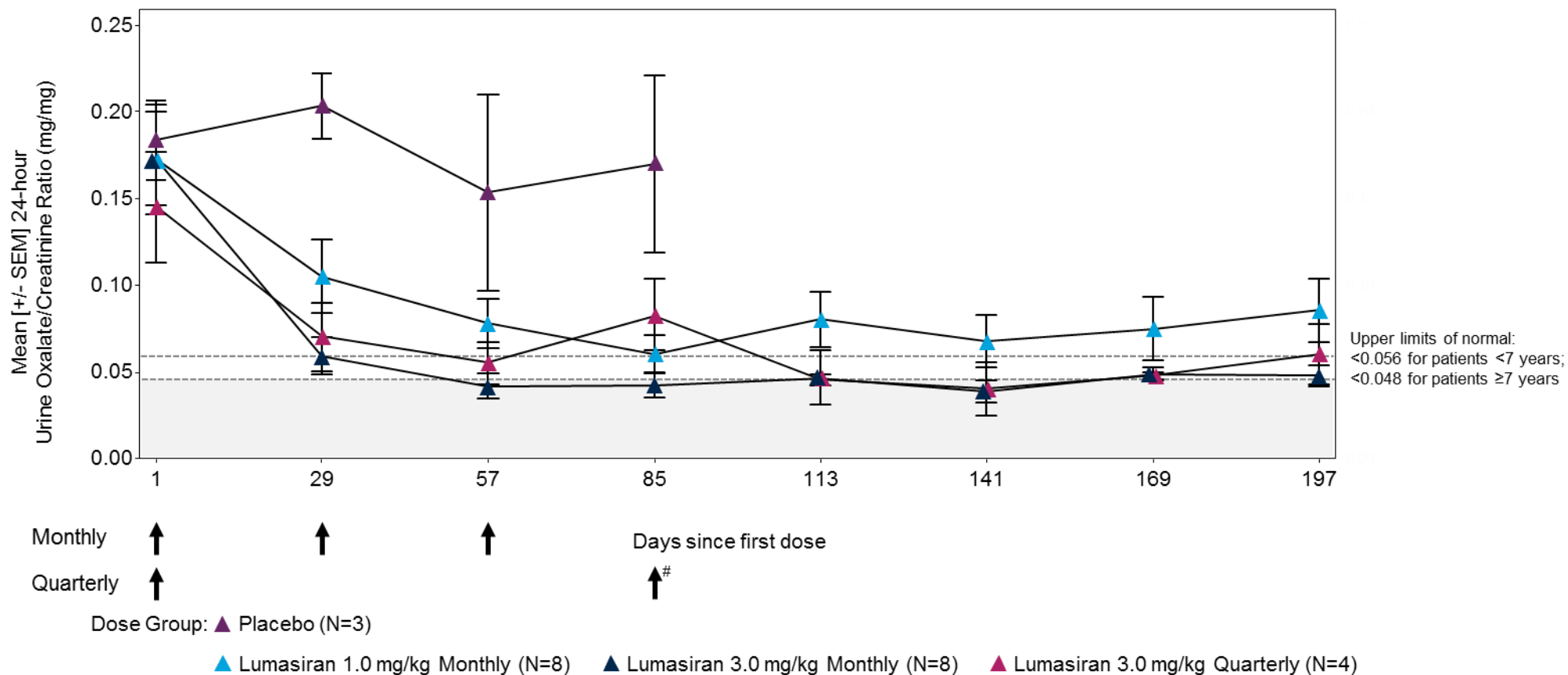
| Urinary Oxalate Reduction | Result |
|---|--------------|
| Mean reduction 28 days post last dose of lumasiran (N=20) | 66% |
| 1.0 mg/kg monthly (N=8) | 66% |
| 3.0 mg/kg monthly (N=8) | 68% |
| 3.0 mg/kg quarterly (N=4) | 63% |
| Patients achieving <0.46 [upper limit of normal] | 13/20 (65%) |
| 1.0 mg/kg monthly | 3/8 (38%) |
| 3.0 mg/kg monthly | 6/8 (75%) |
| 3.0 mg/kg quarterly | 4/4 (100%) |
| Patients achieving <0.69 [1.5x upper limit of normal] | 20/20 (100%) |

Among patients receiving 3.0 mg/kg monthly or quarterly doses of lumasiran, 10/12 (83%) achieved urinary oxalate levels within the normal range

Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Urinary Oxalate/Creatinine Ratio in Part B (Patients with PH1)

Mean maximal reduction in urinary oxalate/creatinine ratio of 76% after lumasiran dosing in all cohorts (N=20)



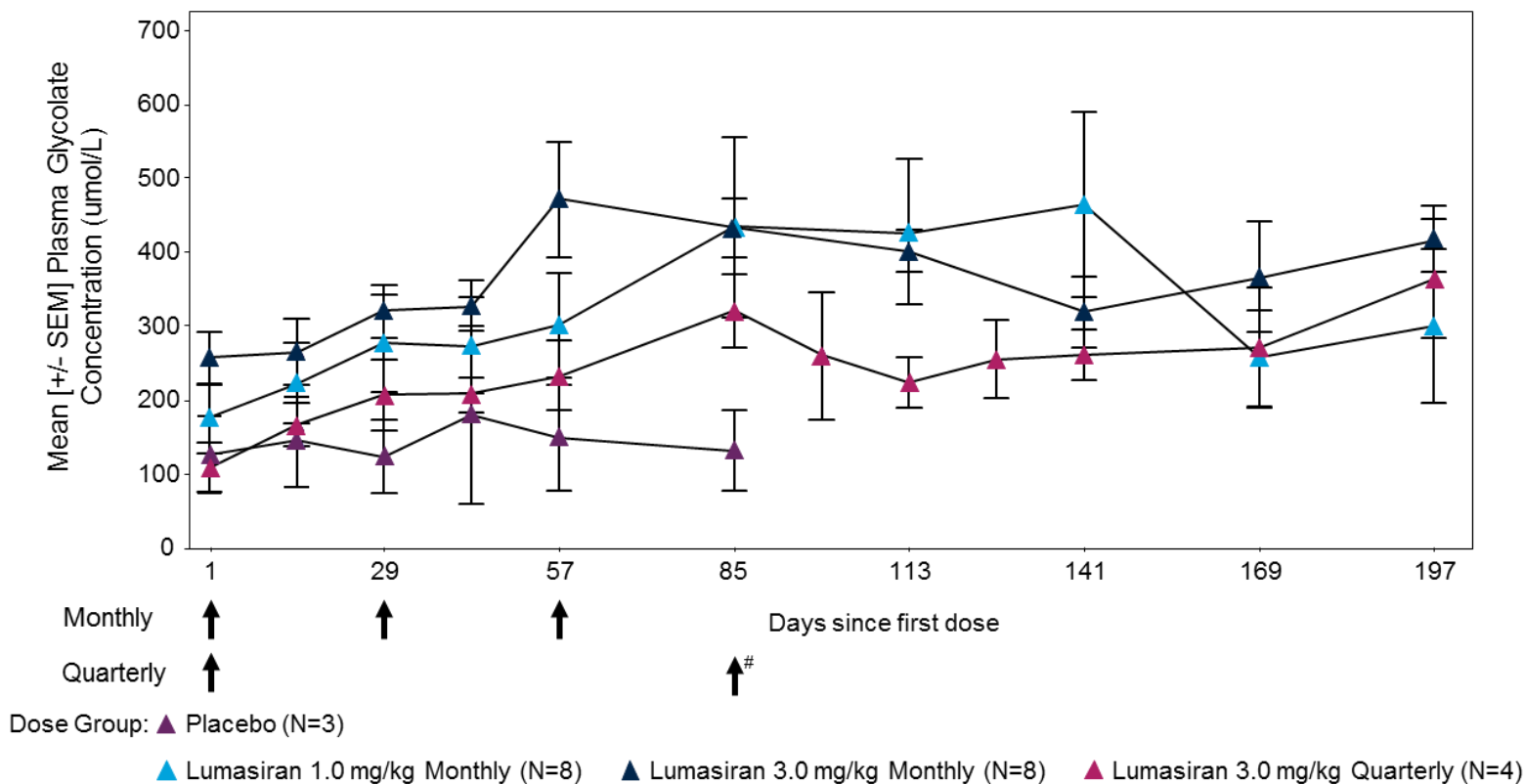
*Data cut-off: 15 Aug 2018

#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

Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Plasma Glycolate in Part B (Patients with PH1)

Consistent with the pharmacology of lumasiran and results from healthy volunteers in Part A¹ of the study, plasma glycolate levels increased in patients receiving lumasiran



Clinical effects of increased glycolate levels have not been reported

*Data cut-off: 15 Aug 2018

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

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ILLUMINATE-A

ILLUMINATE–A*: Phase 3 Study to Evaluate the Efficacy and Safety of Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1

Now Enrolling

Patient population

N=30

- Adults and children ≥ 6 years
- Urinary oxalate excretion ≥ 0.7 mmol/24h/1.73m²
- Confirmed alanine glyoxylate aminotransferase (AGXT) mutations
- eGFR >45 mL/min/1.73m²

2:1 Randomization

6-Month Double Blind Treatment Period

Lumasiran

Three monthly loading doses then maintenance dose of 3.0 mg/kg[†]

Placebo

Equivalent volume for 3 monthly loading doses then maintenance dose

54-month Extension Period

Lumasiran

3.0 mg/kg every 3 months (following loading doses for patients previously receiving placebo)

Primary Analysis at 6 months:

Primary Endpoint : Percent change in 24-hour urinary oxalate excretion

Secondary Endpoints: Change in 24-hour urinary oxalate:creatinine ratio; proportion of patients with 24-hour urinary oxalate level below ULN and 1.5xULN; change in eGFR

Future studies will include a broader population including patients of younger ages and with more severe manifestations of PH1, including renal failure and systemic oxalosis

*NCT03681184; EudraCT Number: 2018-001981-40

[†]3.0 mg/kg once monthly for 3 consecutive months (monthly for 3 doses: loading dose phase)

followed by 3.0 mg/kg once every 3 months (maintenance phase) starting 1 month after the last loading dose.

eGFR, estimated glomerular filtration rate; Month, 28 days; PH1, primary hyperoxaluria type 1; ULN, upper limit of normal



Lumasiran Phase 1/2 Initial Study Results*

Summary and Next Steps

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

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

Adult and pediatric patients receiving lumasiran experienced clinically significant and sustained reductions in urinary oxalate to normal or near normal levels; patients are actively transitioning to continue dosing in the open-label extension study of lumasiran

Multiple doses of lumasiran have demonstrated an acceptable safety profile in patients with PH1 with no discontinuations from study or drug related SAEs; increased glycolate levels were not associated with any safety findings

Data support the therapeutic hypothesis of RNAi mediated inhibition of glycolate oxidase to alleviate pathologic overproduction of oxalate and the continued development of lumasiran across spectrum of patients with PH1 in the Phase 3 ILLUMINATE# trials

*Data cut-off: 15 Aug 2018

RNAi, RNA interference; SAE, serious adverse event; ULN, upper limit of normal

#NCT03681184

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ALN-GO1-001 Investigators

| | | |
|------------------|-------------------|--------------------|
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