



**Safety and Efficacy Study of Lumasiran (ALN-GO1), an Investigational RNA Interference (RNAi) Therapeutic, in Patients with Primary Hyperoxaluria Type 1**

# Primary Hyperoxaluria Type 1

## Rare Genetic Disorder of Increased Endogenous Oxalate Synthesis

### Primary Hyperoxaluria Type 1 (PH1):

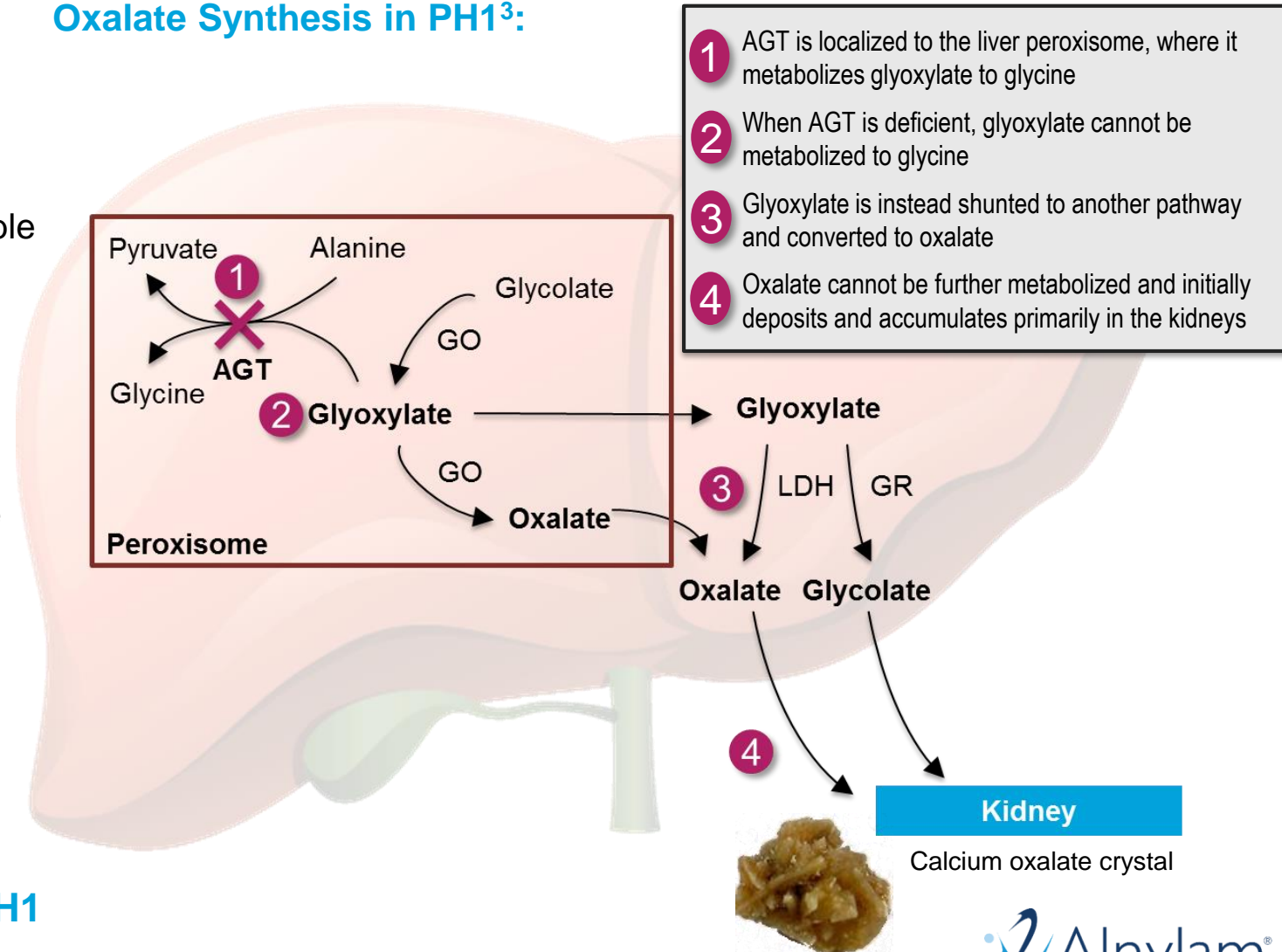
- Due to defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- Phenotype varies significantly in patients and may present at any age, typically in childhood, with variable rates of progression
- Prevalence of PH1: 1-3/1,000,000 in Europe<sup>1</sup> and ~ 32/1,000,000 in Middle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

### Pathophysiology<sup>1</sup>:

- 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 PH1<sup>3</sup>:



# Lumasiran

## Investigational RNAi Therapeutic for Primary Hyperoxaluria Type 1

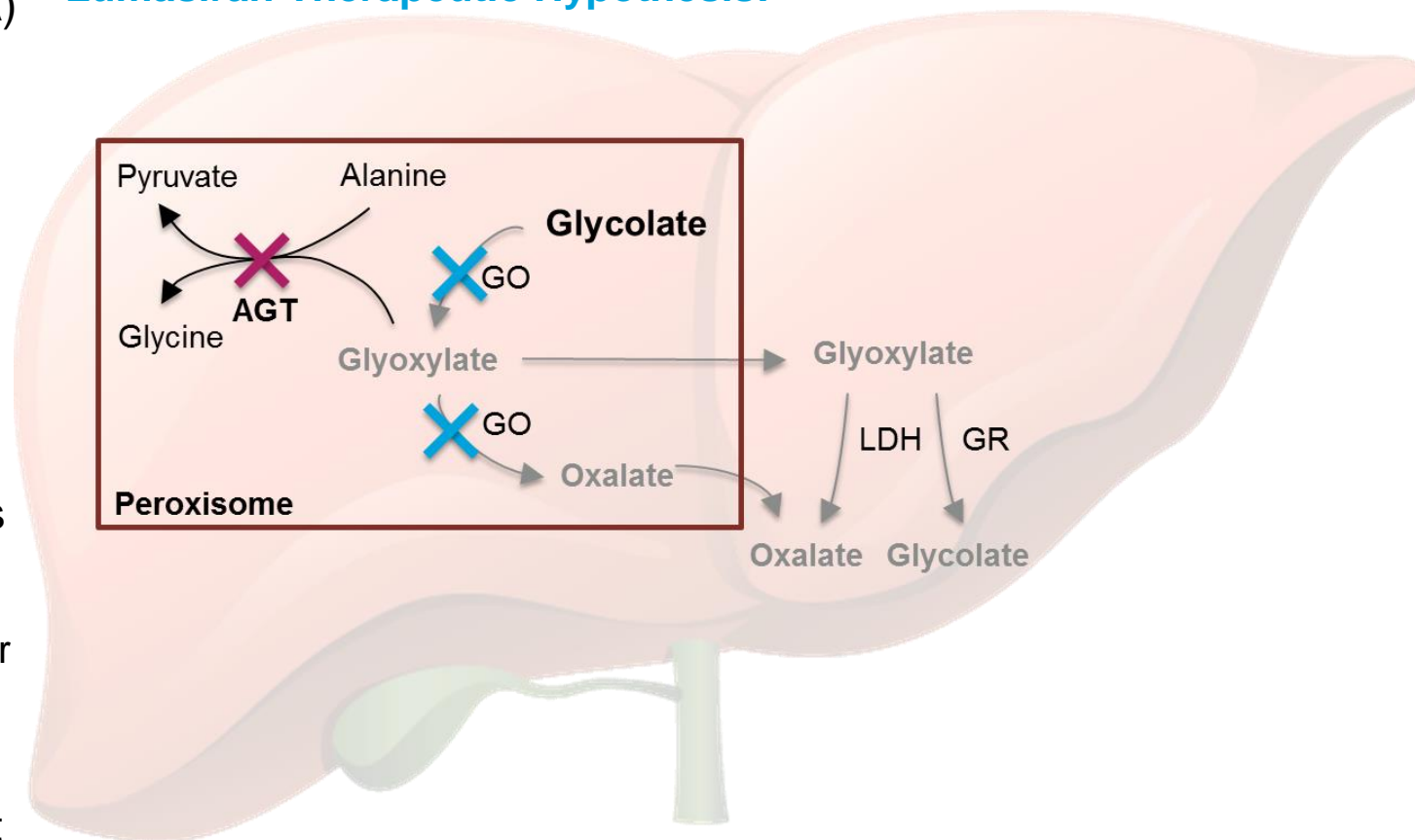
### Lumasiran (ALN-GO1):

- 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 inactivity<sup>1-4</sup>
- 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 findings<sup>5-6</sup>

### Lumasiran Therapeutic Hypothesis:





# Lumasiran Phase 1/2 and Phase 2 Open-Label Extension (OLE)

## Study Design

**Patients previously dosed in Phase 1/2<sup>†</sup> study may be eligible to enroll into Phase 2 OLE<sup>^</sup> study**

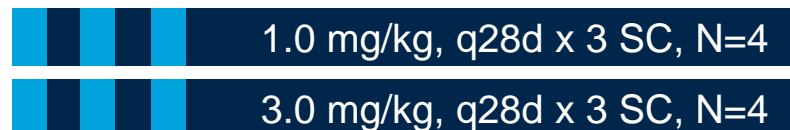
- All patients who have completed follow up in Phase 1/2 have enrolled to continue dosing in OLE\*
- Patients who have been dosed in the OLE (N=8) have been on study for a median of 2.7 months (range: 0.03–3.02)
- Remaining Phase 1/2 patients anticipated to continue dosing in OLE by end of the year

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

**Multiple-Ascending Dose (MAD) | Randomized 3:1, Placebo-controlled<sup>†</sup>**



## Expansion Cohorts | Open-label



## Phase 2 OLE

3.0 mg/kg, q28d SC, N=1

3.0 mg/kg, q84d SC, N=7

**Inclusion Criteria:** Patients with PH1, ages 6-64 years, eGFR > 45 ml/min/1.73m<sup>2</sup>, urinary oxalate excretion ≥ 0.70 mmol/24h/1.73m<sup>2</sup>

\*Data cut-off: 3 Oct 2018

<sup>†</sup>ClinicalTrials.gov Identifier: NCT02706886; EudraCT Number: 2015-004407-23

<sup>^</sup>ClinicalTrials.gov Identifier: NCT03350451; EudraCT Number: 2016-003134-24

# 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 <sup>2</sup> (range)	77 (42–131)
Mean Urine Oxalate Content, mmol/24hr/1.73m <sup>2</sup> (range)	1.69 (0.83–2.97)
Mean Plasma Oxalate Content, µmol/L (range) (N=14 <sup>†</sup> )	8.8 (1.6–19.8)
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)

\*Data cut-off: 15 Aug 2018

<sup>†</sup>Not all patients had plasma oxalate assessments due to insufficient sample  
PH1, primary hyperoxaluria type 1; eGFR, estimated glomerular filtration rate  
Frishberg Y et al. Pediatr Nephrol. 2018 (Abstracts – 51<sup>st</sup> ESPN Meeting, Antalya, Tukey, October 2018)

# Lumasiran Phase 1/2 Study\*

## Disease Characteristics at Study Entry

Characteristic	Result
Time from first symptoms to diagnosis of PH1, mean (years <sup>†</sup> ) (N=13)	1.1 (range: -0.3–5.1)
Time from PH1 diagnosis to first dose of lumasiran, mean (years <sup>†</sup> ) (N=20)	11.3 (range: 2.7–30.8)
Time from first symptoms of PH1 to first dose of lumasiran, mean (years <sup>†</sup> ) (N=13)	13.1 (range: 3.9–34.8)
Results of AGXT Genetic Testing, N (%)	20 (100)
Biallelic Missense, N (%)	9 (45)
Biallelic Frameshift, N (%)	5 (25)
Biallelic Nonsense, N (%)	2 (10)
Others, N (%)	4 (20)

\*Data cut-off: 15 Aug 2018

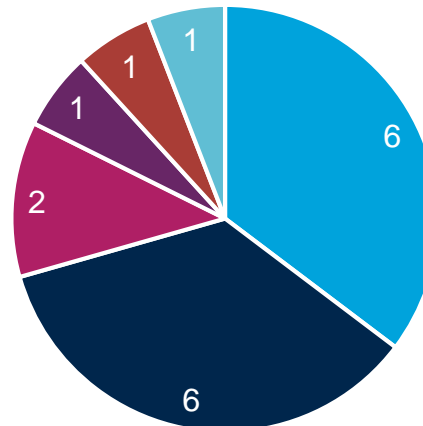
<sup>†</sup>Any incomplete dates of diagnosis or first symptom where day is unknown but month and year known were imputed to be the first day of the month  
PH1, primary hyperoxaluria type 1

# Lumasiran Phase 1/2 Study\*

## Disease Characteristics at Study Entry

Characteristic	Result (N=20)
Patients receiving pyridoxine therapy, N (%)	13 (65)
Mean baseline urinary oxalate content in patients receiving pyridoxine, mmol/24hr/1.73m <sup>2</sup>	1.80 (range: 0.83–2.97)
Patient history of symptoms at study entry, N (%)	
Renal stones	18 (90)
Nephrocalcinosis	13 (65)
Urinary Tract Infection	9 (45)
Pyelonephritis	8 (40)

**Patients with ≥1 symptom present at diagnosis,  
by symptoms (N=17)**



- Renal stone
- Renal stone & nephrocalcinosis
- Nephrocalcinosis & other
- Nephrocalcinosis
- Renal stone, nephrocalcinosis & other
- Renal stone & other

Other includes UTI, polyuria and leukocyturia

# 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 in 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 2 OLE Study Initial Results\*

## Safety

### Continued dosing with lumasiran was well tolerated in patients with PH1

- No discontinuations from study treatment
- SAEs reported in 2/8 patients (25%); none assessed as related to study drug
  - 1 patient with traumatic brain injury and contusion<sup>†</sup>; 1 patient with nephrolithiasis<sup>#</sup>
- AEs reported in 5/8 (63%) of patients
  - AEs were mild or moderate in severity and majority were assessed as unrelated to study drug
- No injection site reactions were reported
- No clinically significant laboratory changes

\*Data cut-off: 3 Oct 2018

<sup>†</sup>SAE of traumatic brain injury and contusion was sustained during a car accident

<sup>#</sup>SAE of nephrolithiasis occurred prior to patient receiving first lumasiran dose in OLE study

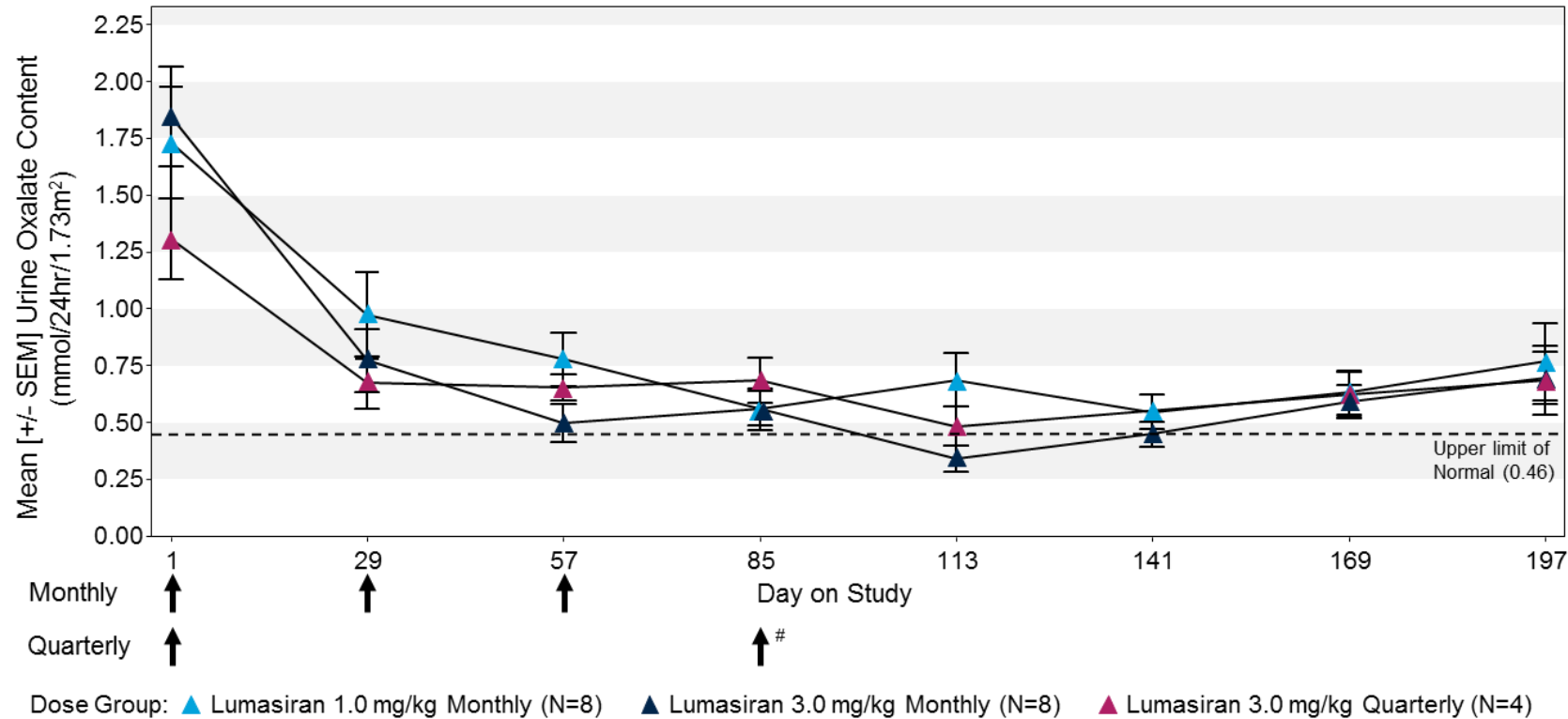
OLE, open-label extension; PH1, primary hyperoxaluria type 1; SAE, serious adverse event; AE, adverse event

# 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

Frishberg Y et al. Pediatr Nephrol. 2018 (Abstracts – 51<sup>st</sup> ESPN Meeting, Antalya, Tukey, October 2018)

# 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**

\*Data cut-off: 15 Aug 2018

PH1, primary hyperoxaluria type 1

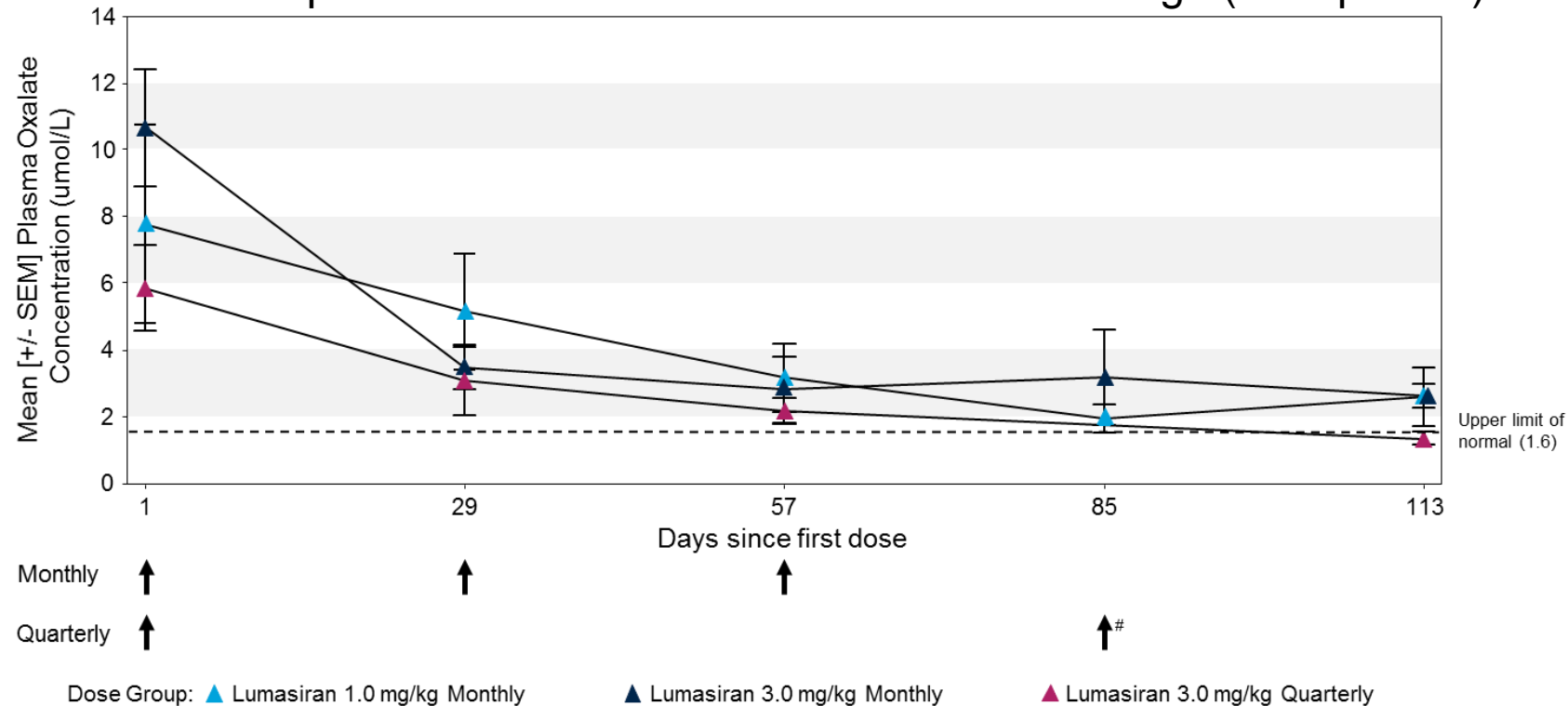
Frishberg Y et al. Pediatr Nephrol. 2018 (Abstracts – 51<sup>st</sup> ESPN Meeting, Antalya, Turkey, October 2018)

# Lumasiran Phase 1/2 Study Initial Results\*

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

**The mean reduction relative to baseline 28 days post last dose of lumasiran was 59% (N=10<sup>†</sup>)**

- Mean maximal reduction in plasma oxalate of 75% (range: 57-94%) relative to baseline after lumasiran dosing
- 50% of patients achieved plasma oxalate levels within the normal range (<1.6  $\mu\text{mol/L}$ )



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

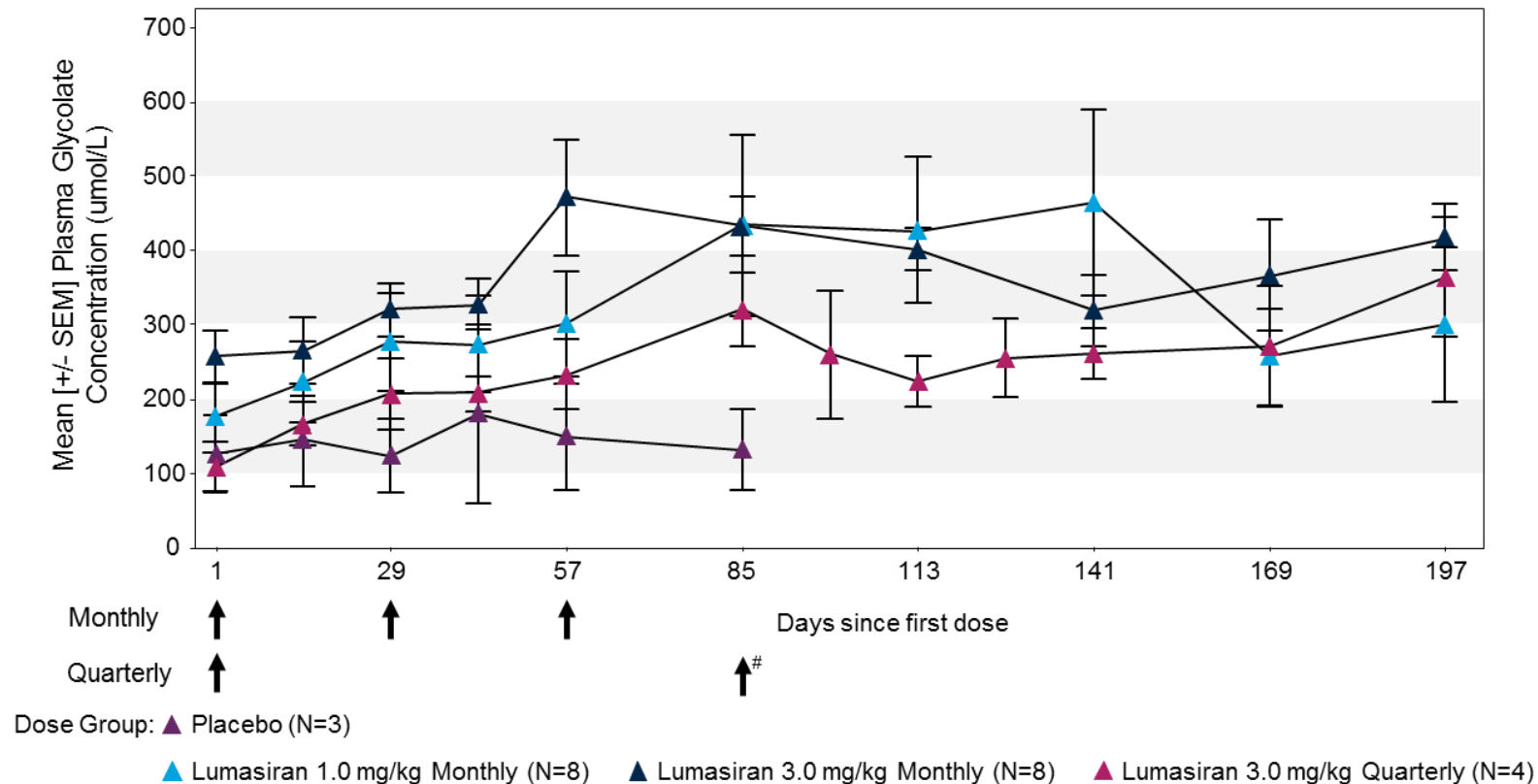
<sup>†</sup>Not all patients had plasma oxalate assessments due to insufficient sample; results reported as <1  $\mu\text{mol/L}$  assigned value of 1

<sup>#</sup>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 A<sup>1</sup> of the study, plasma glycolate levels increased in patients with PH1 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]

#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

Frishberg Y et al. Pediatr Nephrol. 2018 (Abstracts – 51<sup>st</sup> ESPN Meeting, Antalya, Tukey, October 2018)





# 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  $\geq 6$  years
- Urinary oxalate excretion  $\geq 0.7$  mmol/24h/1.73m<sup>2</sup>
- Confirmed alanine glyoxylate aminotransferase (AGXT) mutations
- eGFR  $>45$  mL/min/1.73m<sup>2</sup>

2:1 Randomization

## 6-Month Double Blind Treatment Period

### Lumasiran

Three monthly loading doses then maintenance dose of 3.0 mg/kg<sup>†</sup>

### 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 planned 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

<sup>†</sup>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 Study Initial Results\*

## Summary and Planned 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 progressive 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**

**Patients with all types of AGXT mutations receiving lumasiran experienced clinically significant and sustained reductions in urinary and plasma oxalate to normal or near normal levels**

- Plasma oxalate results confirm urinary oxalate data and the therapeutic hypothesis of lumasiran in decreasing hepatic production of oxalate
- Substantial reduction also seen in patients with elevated urinary oxalate levels despite receiving pyridoxine therapy

**All patients who have completed follow-up in Phase 1/2 have enrolled to continue dosing of lumasiran in the OLE study†**

**Multiple doses of lumasiran 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**

**Phase 3 ILLUMINATE-A# trial is now enrolling and further studies in a broader patient population are planned**

\*Data transfer as of: 15 Aug 2018

†Data transfer as of: 3 Oct 2018

RNAi, RNA interference; OLE, open-label extension SAE, serious adverse event

#NCT03681184