Phase 1/2 Study of Lumasiran, Investigational RNAi Therapeutic, in Patients with Primary Hyperoxaluria Type 1

Yaacov Frishberg[1], Georges Deschênes[2], Jaap Groothoff[3], Sally Hulton[4], Daniella Magen[5], Jérôme Harambat[6], Bernd Hoppe[7], William van't Hoff[8], Dawn Milliner[9], John Lieske[9], Patrick Haslett[10], Sandeep Talamudupula[10], David V. Erbe[10], Tracy L. McGregor[10], Pierre Cochat[11]

[1]Shaare Zedek Medical Center, Pediatric Nephrology, Jerusalem, Israel; [2]Hospital Robert Debre, Pediatric Nephrology, Paris, France; [3]Amsterdam UMC, Pediatric Nephrology, Amsterdam, The Netherlands; [4]Birmingham Children's Hospital, Pediatric Nephrology, Birmingham, United Kingdom; [5]Rambam Health Care Campus, Pediatric Nephrology, Haifa, Israel; [6]Bordeaux University Hospital, Pediatric Nephrology, Bordeaux, France; [7]University Hospital Bonn, Pediatric Nephrology, Bonn, Germany; [8]Great Ormond Street Hospital, Pediatric Nephrology, London, United Kingdom; [9]Mayo Clinic, Nephrology and Hypertension, Rochester, United States; [10]Alnylam Pharmaceuticals, Cambridge, United States; [11]Université Claude Bernard, Centre de Référence des Maladies Rares Néphrogones, Lyon, France

Background and Rationale

Primary Hyperoxaluria Type 1 (PH1):

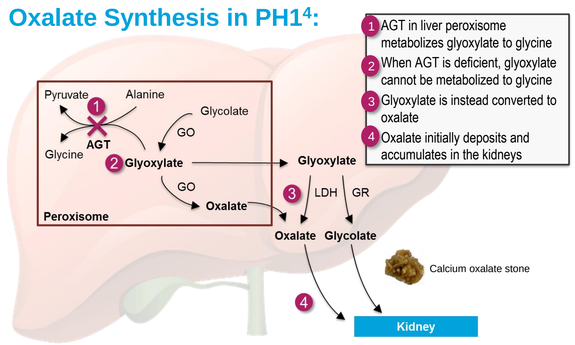
Disease Background:

- 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

Oxalate Synthesis in PH1[4]:



Lumasiran (ALN-GO1)[3]:

Subcutaneously-administered small interfering RNA (siRNA)

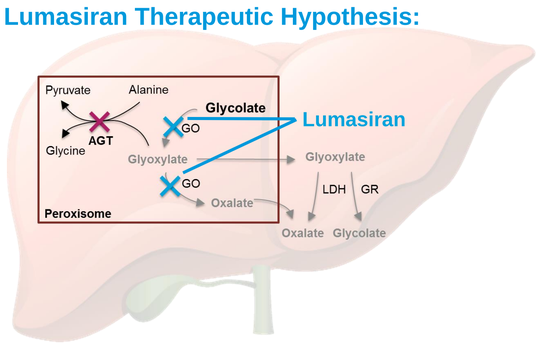
- Harnesses natural RNA interference (RNAi) mechanism

Therapeutic Hypothesis:

- Lumasiran targets the mRNA for *HAO1* which encodes glycolate oxidase (GO) in the liver; the decreased production of GO reduces hepatic oxalate production

No therapies are approved for treatment of PH1

Lumasiran Therapeutic Hypothesis:



The safety and efficacy of lumasiran have not been evaluated by the U.S. Food and Drug Administration (FDA) or any other health agencies

Methods

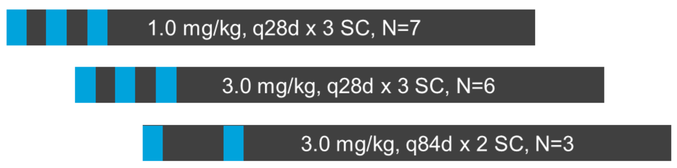
Lumasiran Phase 1/2 Study†

Study Design: Part B
(Patients with PH1; N=20)

A subgroup analysis on patients <18 years old at screening was conducted and reported here (N=16)

Multiple-Ascending Dose (MAD) (N=16)

Randomized 3:1, Single-blind, Placebo-controlled



Inclusion Criteria:

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

Key Endpoints:

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

Patients randomized to placebo received subsequent dosing of lumasiran

After median follow up of 9.8 months (range: 5.6 – 15.2), all patients enrolled in an open-label extension (OLE) study# for long-term dosing*

†NCT02706886; #NCT03350451; *Phase 2 OLE data cut-off 8 Feb 2019; 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

Results

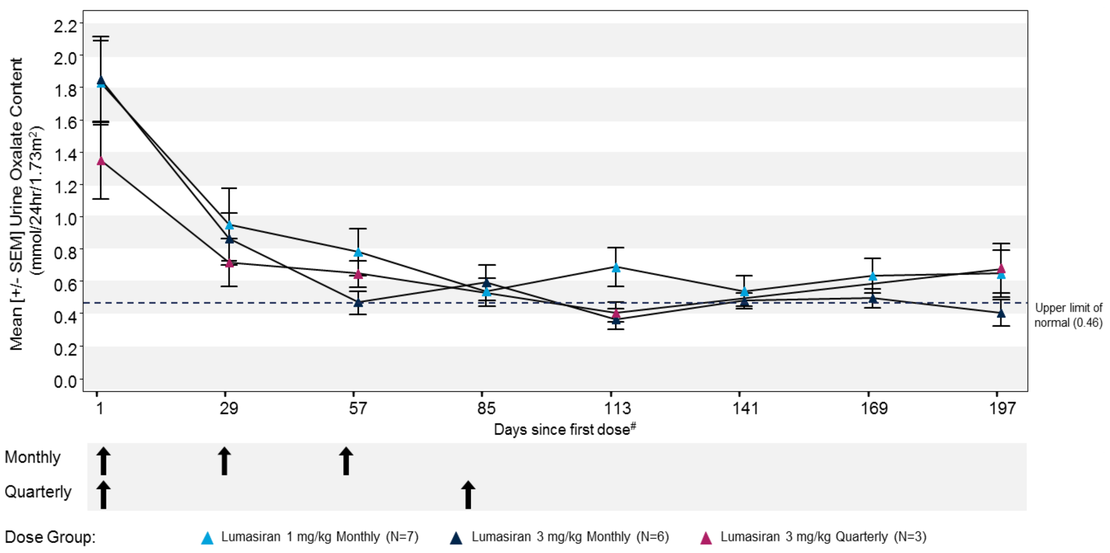
Patient Demographics: Phase 1/2 Part B (Patients with PH1) – Pediatric Cohort

Baseline Characteristics	Result (N=16)
Mean age, years (range)	10.6 (6–17)
Gender, females	75%
Mean weight, kg (range)	39.4 (21.3–82.0)
Mean eGFR, mL/min/1.73m^2 (range)	81.8 (51.7–130.7)
Mean Urine Oxalate Content, mmol/24hr/1.73m^2 (range)	1.75 (0.83–2.97)
Mean 24-hour Urine Oxalate:Creatinine Ratio (range)	0.18 (0.07–0.30)

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

Mean maximal reduction in urinary oxalate of 77% (range: 64-92%) relative to baseline after lumasiran dosing in all cohorts† (N=16)

- The mean reduction relative to baseline 28 days post last dose of lumasiran was 68%†
- 100% of patients achieved a urinary oxalate level ≤1.5x ULN and 75% of patients achieved a urinary oxalate level within the normal range‡
  - Among patients receiving 3.0 mg/kg monthly or quarterly doses of lumasiran, 9/9 (100%) achieved urinary oxalate levels within the normal range



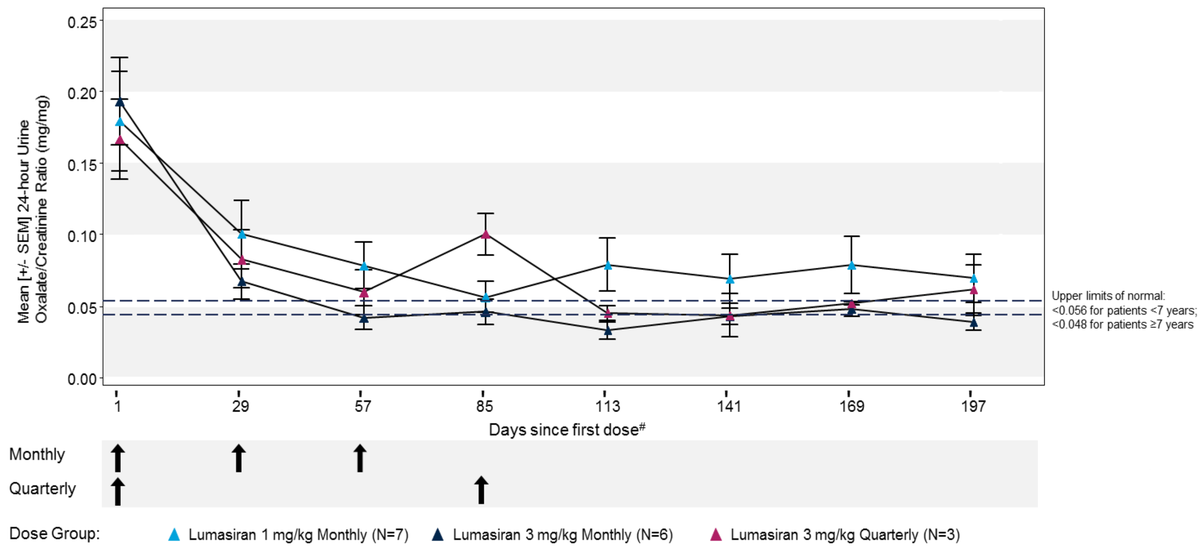
Safety: Phase 1/2 Part B (Patients with PH1) – Pediatric Cohort

Multiple doses of lumasiran were well tolerated

- No discontinuations from study treatment
- SAEs reported in 1 (50%) patient during placebo dosing and 4 (25%) patients after lumasiran dosing; none considered related to study drug by investigator
  - Placebo: 1 patient with acute pyelonephritis and nephrolithiasis
  - Lumasiran: 1 patient with kidney stones; 1 patient with vomiting; 1 patient with gastroenteritis; and 1 patient with abdominal pain, fever and vomiting
- AEs reported in 2 (100%) patients during placebo dosing and 16 (100%) patients after lumasiran dosing
  - Majority of AEs were mild or moderate in severity and considered unrelated to study drug by investigator
  - Severe AEs reported: 1 (50%) placebo patient (acute pyelonephritis) and 1 (6.3%) lumasiran treated patient (nephrolithiasis); these were considered unrelated by investigators
  - AEs reported in >3 patients receiving lumasiran: pyrexia (N=6); cough, abdominal pain, headache, vomiting (N=5 each); nephrolithiasis (N=4)
  - Self-limiting injection site reactions (ISRs) reported in 2 (16.5%) patients receiving lumasiran; all mild and none affected dosing
- No clinically significant laboratory changes

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

Mean maximal reduction in urinary oxalate:creatinine ratio of 79% (range: 50-95%) after lumasiran dosing in all cohorts (N=16)



Lumasiran Phase 2 Open Label Extension Study: Summary of Initial Results (All Patients with PH1)*

Patients have been on OLE for a median of 4 months (range: 0.03–8.36; N=18)

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

Only data points with at least 3 contributing patients are represented.
†Patients who had a valid 24-hour urinary oxalate assessment; placebo data not shown due to limited valid collections
‡1.5x ULN is defined as 0.69 mmol/24hr/1.73m^2; normal range is defined as ≤0.46 mmol/24hr/1.73m^2
#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
*Data cut-off: 8 Feb 2019; †Patients who had a valid 24-hour urinary oxalate at or after Day 85

Summary and Next Steps

- **Lumasiran (ALN-GO1) is a subcutaneously administered investigational RNAi therapeutic specifically designed to reduce hepatic production of oxalate in patients with PH1**
- **Pediatric patients receiving lumasiran experienced clinically significant and sustained reductions in urinary oxalate to normal or near normal levels**
- **Safety and efficacy of lumasiran observed in pediatric patients is consistent with the overall patient population**
- **Multiple doses of lumasiran have demonstrated an acceptable safety profile in patients with PH1 with no discontinuations from study or drug related SAEs**
- **Data support the therapeutic hypothesis and the continued development of lumasiran across a spectrum of patients with PH1 in the Phase 3 ILLUMINATE# trials**

ILLUMINATE

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

ILLUMINATE–B§
A Phase 3 Single Arm Study to Evaluate the Efficacy and Safety of Lumasiran in Infants and Young Children with Primary Hyperoxaluria Type 1

#NCT03681184; NCT03905694; *NCT03681184, EudraCT Number: 2018-001981-40; §NCT03905694, EudraCT Number: 2018-004014-17

References: 1. Cochat P, et al. *New Engl J Med.* 2013. 2. Abumwais JQ, et al. *Saudi J Kid Dis Transpl.* 2012. 3. Liebow A, et al. *J Am Soc Nephrol.* 2017. 4. Cochat P. *Kidney Int*. 1999.

Disclosures. Study sponsored by Alnylam.

AGT, alanine:glyoxylate aminotransferase; eGFR, estimated glomerular filtration rate; FDA, food and drug administration; GO, glycolate oxidase; *HAO1*, hydroxyacid oxidase 1; MAD, multiple-ascending dose; Month, 28 days; OLE, open label extension; PH1, primary hyperoxaluria type 1; RNAi, RNA interference; SAE, serious adverse event; siRNA, small interfering RNA; ULN, upper limit of normal