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

**Yaacov Frishberg**, William van't Hoff, Sally Hulton, Patrick Haslett, David V. Erbe, Tracy McGregor, Georges Deschênes

1Shaare Zedek Medical Center, Jerusalem, Israel; 2Great Ormond Street Hospital, London, United Kingdom; 3Birmingham Childrens’ Hospital, Birmingham, United Kingdom; 4Alnylam Pharmaceuticals, Cambridge, MA, United States; 5Hospital Robert Debre, Paris, France.
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\(^2\)

---

Background
Systemic Oxalosis in PH1

Abdominal X-ray with nephrocalcinosis bilaterally

Patient with bone deformities secondary to pathologic fractures

Histology of bone marrow with multiple calcium oxalate crystals

Retinal oxalosis

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
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

- 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, Iguacu, Brazil]
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.**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Details</th>
<th>Additional Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 year old boy¹</td>
<td>Marked elevations of urinary glycolate</td>
<td>Healthy liver and healthy kidneys; Triple A-like Syndrome (GMPPA)</td>
</tr>
<tr>
<td></td>
<td>Homozygous deleterious <em>HAO1</em> mutation</td>
<td></td>
</tr>
<tr>
<td>14 month old boy²</td>
<td>Marked elevations of urinary glycolate</td>
<td>Healthy liver and healthy kidneys; <em>HAO1</em> not sequenced</td>
</tr>
<tr>
<td></td>
<td>Normal AGT activity on liver biopsy</td>
<td></td>
</tr>
<tr>
<td>Adult woman³</td>
<td>Homozygous <em>HAO1</em> mutation detected as part of broad sequencing effort</td>
<td>Healthy liver and kidneys; Three healthy pregnancies</td>
</tr>
<tr>
<td>9 month infant girl⁴</td>
<td>Congential Hyperinsulinism (<em>ABCC8</em>)</td>
<td>Elevated oxalate in spot urines; Negative sequencing for PH1/PH2/PH3</td>
</tr>
<tr>
<td></td>
<td>Marked elevations of urinary glycolate</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>HAO1</em> mutations detected</td>
<td></td>
</tr>
</tbody>
</table>

AGT, alanine:glyoxylate aminotransferase; GO, glycolate oxidase; PH, primary hyperoxaluria
Lumasiran Phase 1/2 Study*
Study Design & Demographics: Part B (Patients with PH1)

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

- 1.0 mg/kg, q28d x 3 SC, N=4
- 3.0 mg/kg, q28d x 3 SC, N=4
- 3.0 mg/kg, q84d x 2 SC, N=4

Population: PH1 patients, ages 6-64 years; eGFR>45 ml/min/1.73m²; Urinary oxalate excretion ≥ 0.70 mmol/24h/1.73m²
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
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/1.73m² in all patients with baseline excretion ≥ 1.6 mmol/24hr/1.73m²

Renal survival was examined by quartile of urine oxalate (UOx) excretion (mmol/24hr/1.73m²) 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.
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

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

ALN-GO1-001 Investigators

Reham Almardini  Jérôme Harambat  Ulrike Lorch
Pierre Cochat  Bernd Hoppe  Daniella Magen
George Deschenes  Sally-Anne Hulton  Dawn Milliner
Yaacov Frishberg  John Lieske  Shabbir Moochhala
Jaap Groothoff  Graham Lipkin  William Van’t Hoff

Collaborations

Born in Bradford Study
Mayo Laboratories