Final Results from the Phase 1/2 Trial of Lumasiran and Program Updates

Tracy McGregor, MD
Alnylam Pharmaceuticals
**Lumasiran**

Investigational RNA interference Therapeutic for Primary Hyperoxaluria Type 1 (PH1)

**Lumasiran (ALN-GO1):**
- SC-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

**Lumasiran Therapeutic Hypothesis:**

![Diagram of Lumasiran action](attachment:image)

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

HAO1, hydroxyacid oxidase 1
## 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**

Patients randomized to placebo received subsequent dosing of lumasiran

### Expansion Cohorts | Open-label

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

**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

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

eGFR, estimated glomerular filtration rate
## Lumasiran Phase 1/2 Study
### Patient Demographics: Part B (Patients with PH1)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Result (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>14.9 (6–43)</td>
</tr>
<tr>
<td>Age &lt;18 years</td>
<td>80%</td>
</tr>
<tr>
<td>Gender, females</td>
<td>65%</td>
</tr>
<tr>
<td>Mean weight, kg (range)</td>
<td>50.0 (21.3–112.5)</td>
</tr>
<tr>
<td>Mean eGFR, mL/min/1.73m² (range)</td>
<td>77.3 (42.5–130.7)</td>
</tr>
<tr>
<td>Mean Urine Oxalate Content, mmol/24hr/1.73m² (range)</td>
<td>1.69 (0.83–2.97)</td>
</tr>
<tr>
<td>Mean 24-hour Urine Oxalate:Creatinine Ratio (range)</td>
<td>0.17 (0.07–0.30)</td>
</tr>
</tbody>
</table>

*Mean age, estimated glomerular filtration rate (eGFR)*
Lumasiran Phase 1/2 Study 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 4 (20%) patients after lumasiran dosing; none considered related to study drug by investigator
  – Placebo: 1 patient with SAEs of acute pyelonephritis and kidney stones
  – 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 (66.7%) patients during placebo dosing and 20 (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 (33%) patient during placebo dosing (acute pyelonephritis) and 1 (5%) patients after lumasiran dosing (kidney stone); none considered related to study drug by investigator
  – AEs reported in >3 patients receiving lumasiran: pyrexia (N=6); vomiting, cough, abdominal pain, headache (N=5 each); and rhinitis and nephrolithiasis (N=4 each)
  – Self-limiting injection site reactions (ISRs) reported in 3 (15%) patients receiving lumasiran; all mild or moderate and none affected dosing
• No clinically significant laboratory changes
**Lumasiran Phase 1/2 Study Results**

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

Mean maximal reduction in urinary oxalate of 75% (range: 43-92%) 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%
- 100% of patients achieved a urinary oxalate level ≤1.5x ULN and 70% of patients achieved a urinary oxalate level within the normal range‡
  - Among patients receiving 3.0 mg/kg monthly or quarterly doses of lumasiran, 11/12 (92%) achieved urinary oxalate levels within the normal range

---

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

Lumasiran Phase 1/2 Study Results

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/1.73m²; normal range is defined as ≤0.46 mmol/24hr/1.73m²

#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

ULN, upper limit of normal
Lumasiran Phase 1/2 Study Results
Pharmacodynamics: Urinary Oxalate:Creatinine Ratio in Part B (Patients with PH1)

Mean maximal reduction in urinary oxalate:creatinine ratio of 77% (range: 50-95%) after lumasiran dosing in all cohorts (N=20)
Lumasiran Phase 2 OLE Study
Summary of Initial Results*

As of February 2019, 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)†

*Data cut-off: 8 Feb 2019; †Patients who had a valid 24-hour urinary oxalate at or after Day 85; #Patients with a urinary oxalate assessment performed in the Phase 1/2 study collected within 30 days before Day 1 were not required to repeat the assessment
Lumasiran Phase 1/2 Study Results

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.

Adult and pediatric patients receiving lumasiran experienced clinically significant and sustained reductions in urinary oxalate to normal or near normal levels.

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.

RNAi, RNA interference; SAE, serious adverse event
#NCT03681184; NCT03905694
**ILUMINATE-A**
A Phase 3 Study to Evaluate the Efficacy and Safety of Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1

**Patient population (N=30)**

**Key Inclusion Criteria:**
- Adults and children ≥6 years
- Urinary oxalate excretion ≥0.7 mmol/24 h/1.73 m²
- Confirmed alanine glyoxylate aminotransferase (AGXT) mutations
- eGFR >30 mL/min/1.73 m²

**2:1 Randomization**

- **Lumasiran**
  - Three monthly loading doses then maintenance dose of 3.0 mg/kg
- **Placebo**
  - Equivalent volume for 3 monthly loading doses then maintenance dose

**6-Month Double-Blind Treatment Period**

**54-Month Extension Period**

**Primary Analysis at 6 Months:**
- **Primary Endpoint:** Percent change in urinary oxalate excretion from baseline (average percent change from baseline across months 3 through 6)
- **Secondary Endpoints:** Change in 24-hour urinary oxalate:creatinine ratio; proportion of patients with 24-hour urinary oxalate level below ULN and 1.5 x ULN; change in eGFR; change in plasma oxalate

**Top line results from this study expected in late 2019**

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

Now Enrolling

Patient population (N=8)

Key Inclusion Criteria:
- Infants and children <6 years
- Elevated urinary oxalate:creatinine ratio
- Confirmed alanine glyoxylate aminotransferase (AGXT) mutation
- eGFR >45 mL/min/1.73 m² if ≥12 months old; non-elevated serum creatinine if <12 months old

Open-Label

Lumasiran
Three monthly loading doses then maintenance dosing dependent on weight†

54-Month
Open-Label Extension Period

Lumasiran
Continued once monthly or every 3 months maintenance dosing based on weight‡

Primary Analysis:
- Primary Endpoint: Percent change in urinary oxalate excretion at 6 months (average percent change from baseline across months 3 through 6)
- Secondary Endpoints: Percent change in urinary oxalate excretion (extension period); absolute change in urinary oxalate excretion; proportion of patients with 24-hour urinary oxalate level below ULN and 1.5xULN; plasma PK of lumasiran; change in eGFR

*NCT03905694; EudraCT Number: 2018-004014-17
†Patients <10 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 3.0 mg/kg. Patients ≥10 kg to <20 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 6.0 mg/kg. Patients ≥20 kg: Three monthly loading doses at 3.0 mg/kg then maintenance dose of 3.0 mg/kg
‡Continued weight-based dosing using weight obtained 7 days prior to dosing
eGFR, estimated glomerular filtration rate; Month, 28 days; PH1, primary hyperoxaluria type 1; ULN, upper limit of normal
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, Bradford Royal Infirmary  
Mayo Laboratories