Results from the Ongoing Phase 2 Open-Label Extension Study of Lumasiran, an Investigational RNAi Therapeutic, in Patients with Primary Hyperoxaluria Type 1 (PH1)

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Disclosures

Y Frishberg: consultancy fees from Alnylam Pharmaceuticals and membership of the SRC

S Hulton: travel expenses to participate in clinical research meetings and consultancy fees paid to Birmingham Children’s Hospital Renal Research Fund from Alnylam Pharmaceuticals

P Cochat: consultancy fees and invitations to scientific meetings from Alnylam Pharmaceuticals

J Groothoff: reports consultancy fees from Alnylam Pharmaceuticals and research grants from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, and UniQure Pharmaceuticals

D Magen: research funding, consultancy fees, and non-financial support from Alnylam Pharmaceuticals

J Harambat: nothing to disclose

G Schalk: nothing to disclose

W van’t Hoff: travel expenses to participate in clinical research meetings and financial recompense for clinical trial participation which was paid to his institute

D LeSueur, T McGregor: employees of Alnylam Pharmaceuticals and D LeSueur, T McGregor: holds shares in Alnylam Pharmaceuticals

G Deschênes: consultancy fees from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, and Biocodex, and was a PI for research funded by OxThera
Primary Hyperoxaluria Type 1 (PH1)

- PH1 is caused by deficiency in hepatic peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- Hepatic overproduction of oxalate leads to recurrent kidney stones, nephrocalcinosis, progressive renal failure, and multiorgan damage from systemic oxalosis (Figure 1)
- Diagnosed prevalence: ~1 to 3 cases per 1 million population, with higher prevalence in parts of the Middle East and North Africa¹,²
- Age and severity of symptoms at diagnosis highly variable¹,³
- No therapies currently approved for PH1 treatment

Figure 1. Oxalate Synthesis in PH1

AGT, alanine:glyoxylate aminotransferase; GO, glycolate oxidase; GR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1

Background and Rationale Continued

Lumasiran (ALN-GO1)¹

• Subcutaneously administered investigational RNA interference (RNAi) therapeutic
• Harnesses natural RNAi mechanism
• Decreases hepatic oxalate production by targeting glycolate oxidase (Figure 2)
• In the Phase 1/2 study in patients with PH1 (NCT02706886), lumasiran demonstrated clinically significant and sustained reductions in urinary and plasma oxalate to normal or near-normal levels, with an acceptable safety profile²

Figure 2. Lumasiran Therapeutic Hypothesis

AGT, alanine:glyoxylate aminotransferase; GO, glycolate oxidase; GR glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1; RNAi, RNA interference

Methods

Patients Completing the Phase 1/2 Study Were Eligible to Enroll in the Phase 2 Open-Label Extension (OLE) Study (NCT03350451)

• All 20 patients enrolled in Phase 1/2 completed the study and enrolled in the OLE
• Data presented here are for all patients dosed in the Phase 2 OLE, as of January 30, 2020
• Dosing for a median of 15 (range: 11–22) months
• Since the data cut, all patients have been transitioned to 3.0 mg/kg q3M

Patients Completing the Phase 1/2 Study Were Eligible to Enroll in the Phase 2 Open-Label Extension (OLE) Study (NCT03350451)

Methods

Phase 1/2 Part B (N=20)
- 1.0 mg/kg, qM × 3 SC, N=8
- 3.0 mg/kg, qM × 2 SC, N=4
- 3.0 mg/kg, qM × 3 SC, N=8

Phase 2 OLE (N=20)
- 1.0 mg/kg, qM → 3.0 mg/kg, q3M SC, N=8
- 3.0 mg/kg, q3M SC, N=5
- 3.0 mg/kg, qM SC, N=7

Inclusion criteria: Ages 6–64 years; eGFR >45 mL/min/1.73m²; urinary oxalate excretion >0.70 mmol/24 h/1.73m²

Oxalate Assay
• All data presented here use a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay developed for Phase 3 studies. Previous presentations of the Phase 1/2 and Phase 2 OLE studies used an enzymatic assay to measure urinary oxalate. Pearson correlation coefficient for the two methods was 0.925
## Results

### Table 1. Patient Demographics and Disease Characteristics (N=20)\(^a\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>16 (7–44)</td>
</tr>
<tr>
<td>Age &lt;18 years</td>
<td>75%</td>
</tr>
<tr>
<td>Female</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/1.73m(^2) (range)</td>
<td>77 (42–131)</td>
</tr>
<tr>
<td>Mean 24-hour urinary oxalate excretion, mmol/24 hr/1.73m(^2) (range)(^a)</td>
<td>2.24 (0.94–5.18)</td>
</tr>
<tr>
<td>Mean 24-hour urinary oxalate:creatinine ratio, mmol/mmol (range)(^a)</td>
<td>0.28 (0.11–0.56)</td>
</tr>
</tbody>
</table>

\(^a\)Baseline disease characteristics are from the derived baseline in Phase 1/2 study

eGFR, estimated glomerular filtration rate
Results

Urinary Oxalate Content in 24-Hour Urinary Collections

• Patients experienced sustained reductions in urinary oxalate excretion, with similar responses between dosage regimens (Figure 3)

• Mean maximal reduction in urinary oxalate of 74.5% (range: 35.7–88.3%) relative to Phase 1/2 baseline (N=17)a

• 17/18a (94.4%) patients achieved normal or near-normal (≤1.5 × ULN)b levels of urinary oxalate

Figure 3. Mean (± SEM) of Actual 24-Hour Urinary Oxalate Values (Corrected for BSA)
Results

Urinary Oxalate:Creatinine Ratio in 24-Hour Urinary Collections

- Patients experienced sustained reductions in urinary oxalate:creatinine ratio, with similar responses between dosage regimens (Figure 4)
- Mean maximal reduction in urinary oxalate:creatinine ratio of 77.5% (range: 55.3–95.8%) (N=20)

Additional Measures

- Plasma oxalate levels decreased (mean maximal reduction 55.2%, N=19)
- Mean eGFR values were stable over time

Figure 4. Mean (± SEM) of Actual Values in 24-Hour Urinary Oxalate:Creatinine Ratio

Initial dose of lumasiran in study

<table>
<thead>
<tr>
<th>Visit</th>
<th>No. of patients:</th>
<th>Initial dose of lumasiran in study</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>N= 13</td>
<td>1.0 mg/kg qM or 3.0 mg/kg q3M (N=13)</td>
</tr>
<tr>
<td>M3</td>
<td>N= 7</td>
<td>3.0 mg/kg qM (N=7)</td>
</tr>
<tr>
<td>M6</td>
<td>N= 20</td>
<td>Total (N=20)</td>
</tr>
<tr>
<td>M9</td>
<td>N= 19</td>
<td></td>
</tr>
<tr>
<td>M12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. of patients:
- N= 13
- N= 7
- N= 20
Results

Safety and Tolerability

- Continued dosing with lumasiran was generally well tolerated in patients with PH1
- Adverse events (AEs) were reported in 19/20 (95.0%) patients; all were mild or moderate in severity and the majority were assessed as unrelated to study drug
- The most common drug-related AEs reported were mild, transient injection-site reactions
- No discontinuations or drug-related serious AEs were reported
- No clinically significant laboratory changes were reported
- No AEs of kidney stones were reported

Table 2. Post hoc Analysis Conducted Based on Data Collected for Renal Stone Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Patients Reporting &gt;1 Renal Stone</th>
<th>Total Number of Renal Stones</th>
<th>Duration of Follow-Up (patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical (prior 12 months)</td>
<td>6/20</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Phase 1/2 Part B</td>
<td>4/20</td>
<td>7</td>
<td>7.8c</td>
</tr>
<tr>
<td>Phase 2 OLE</td>
<td>0/20</td>
<td>0</td>
<td>26.4d</td>
</tr>
</tbody>
</table>

aRenal stones not collected as an efficacy endpoint; any renal stone meeting AE definition is reported and recorded as an AE. Renal stones were identified in AE listings by medical review. bPatients reported number of renal stones in the 12 months prior to enrollment in the Phase 1/2 Study. cFrom first dose to last dose + 84 days. dFrom first dose to data cut-off: January 30, 2020. Interval between Phase 1/2 Part B and Phase 2 OLE not represented in these data.
Conclusions

- During this period of the phase 2 OLE study, lumasiran continues to demonstrate an acceptable safety profile with no discontinuations from study treatment or drug-related serious adverse events.
- Continued therapy with lumasiran maintained reduction of urinary oxalate to levels near or below the upper limit of normal.
- The most common drug-related AEs reported were mild, transient injection-site reactions.
- No adverse events of kidney stones were reported in this OLE period.
- These data provide long-term efficacy and safety with data for up to 22 months of exposure to lumasiran.

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