**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: 1.31/1,000,000 in Europe and ~321,000,000 in Middle East

**Pathophysiology**
- Overproduction of oxalate results in calcium oxalate crystals leading to urolithiasis, nephrocalcinosis, kidney failure, ultimately leading to multi-organ damage from systemic oxalosis
- No therapies are approved for treatment of PH1

**Lumasiran (ALN-GO1):**
- Subcutaneously-administered small interfering RNA (siRNA)
- Harnesses natural RNA interference (RNAi) mechanism
- Therapeutic Hypothesis
  - Lumasiran targets liver hydroxypyruvate oxidase 1 (HAD1), mRNA, decreasing production of glyoxalate (GO), and hence reduces hepatic oxalate production

**Methods**

- Patients completing Phase 1/2 study eligible to enroll into Phase 2 open-label extension (OLE) study
- All patients enrolled in Phase 1/2 completed and enrolled in OLE (N=20)
- All patients have been on study for a median of 10.4 months (range: 7–12, N=20)

**Inclusion Criteria for Phase 2 OLE Study:**
- Patients with PH1
- Ages 6–64 years
- eGFR >45 ml/min/1.73m²
- Urinary oxalate excretion ≥ 0.70 mmol/24h/1.73m²
- Tolerated lumasiran in Phase 1/2 study

**Results Phase 2 OLE Patient Demographics**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Results (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range)</td>
<td>16 (7-44)</td>
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<tr>
<td>Age, years (range)</td>
<td>75%</td>
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<tr>
<td>Gender, females</td>
<td>65%</td>
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<tr>
<td>Mean weight, kg (range)</td>
<td>50.0 (21.3 – 112.5)</td>
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<tr>
<td>Mean eGFR, ml/min/1.73m²</td>
<td>77.42 (131.9)</td>
</tr>
<tr>
<td>Mean Urine Oxalate Content, mmol/24hr/1.73m² (range)</td>
<td>1.69 (0.83 – 2.97)</td>
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<tr>
<td>Mean 24-hour Urine Oxalate:Creatinine Ratio, mg/mg (range)</td>
<td>0.17 (0.07 – 0.35)</td>
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</tbody>
</table>

**Results Continued**

**Urine Oxalate Content in 24-hour urinary collections**
- Patients experienced sustained reductions in urinary oxalate content
- Mean maximal reduction in urinary oxalate at 76% (range: 43-91%) relative to Phase 1/2 baseline in all cohorts (N=19)^1^  
  - 100% of patients achieved a urinary oxalate level ≤ 0.15x ULN and 86% of patients achieved a urinary oxalate level within normal range (N=18)

**Urine Oxalate:Creatinine Ratio in 24-hour urinary collections**
- Patients experienced sustained reductions in urinary oxalate:creatinine ratio
- Mean maximal reduction in urinary oxalate:creatinine ratio of 82% (range: 62-94%) after lumasiran dosing in all cohorts (N=20)

**Lumasiran Therapeutic Hypothesis:**
- The safety and efficacy of lumasiran have not been demonstrated in any other health agencies.

**Summary**
- 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 is a subcutaneously-administered investigational RNAi therapeutic specifically designed to reduce hepatic production of oxalate in patients with PH1
- All patients enrolled in Phase 1/2 study completed the study and elected to continue dosing in the ongoing Phase 2 OLE
- Continued dosing with lumasiran in Phase 2 OLE demonstrated an acceptable safety profile in patients with PH1 with no discontinuations from study treatment or drug-related AEs
- Patients in Phase 2 OLE experienced sustained reductions in urinary oxalate
- Data support the therapeutic hypothesis and continued development of lumasiran across a spectrum of patients with PH1 in the Phase 3 ILLUMINATE trials