ILLUMINATE-A, a Phase 3 Study of Lumasiran, an Investigational RNAi Therapeutic, in Children and Adults with Primary Hyperoxaluria Type 1 (PH1)


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Primary Hyperoxaluria Type 1

Progressive disease mediated by hepatic overproduction of oxalate

- Diagnosed prevalence: ~1 to 3 cases per 1 million population\(^1\)
- >40% of patients with PH1 present with ESKD at diagnosis\(^3\)
- Without effective treatment, PH1 often leads to death from renal failure or complications of oxalosis\(^1,2\)
- Management options include hyperhydration, crystallization inhibitors, symptomatic care for kidney stones, and pyridoxine (vitamin B6) in some patients\(^1,2\)
- Dual liver–kidney transplantation is frequently necessary to normalize hepatic oxalate production and restore renal function\(^1,2\)
- No approved pharmacologic therapies

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AGT, alanine-glyoxylate aminotransferase; AGXT, alanine-glyoxylate aminotransferase gene; ESKD, end-stage kidney disease; PH1, primary hyperoxaluria type 1

Lumasiran

Investigational RNAi therapeutic for PH1

- RNAi is a natural pathway involved in regulation of gene expression by targeting mRNA\(^1\)
- Lumasiran targets the mRNA for HAO1, which encodes GO in the liver\(^1\)
- Decreased production of GO reduces hepatic oxalate production, lowering oxalate levels\(^1\)
- Early phase studies of lumasiran demonstrated an encouraging safety profile and a substantial reduction in urinary oxalate which is expected to confer clinical benefit in patients with PH1\(^2\)–\(^4\)
- ILLUMINATE-A is a randomized, double-blind, placebo-controlled Phase 3 study, designed to evaluate efficacy and safety of lumasiran in children and adults with PH1

AGT, alanine-glyoxylate aminotransferase; GO, glycolate oxidase; GR, glyoxylate reductase/hydroxypyruvate reductase; HAO1, hydroxyacid oxidase gene 1; LDH, lactate dehydrogenase; mRNA, messenger RNA; PH1, primary hyperoxaluria type 1; RNAi, RNA interference

## Lumasiran Clinical Development

<table>
<thead>
<tr>
<th>Phase 1/2</th>
<th>Phase 3</th>
</tr>
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<tr>
<td><strong>STUDY 001</strong></td>
<td><strong>ILLUMINATE-A</strong></td>
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<tr>
<td>Healthy volunteers</td>
<td>PH1 patients</td>
</tr>
<tr>
<td>Part A: single ascending dose, n=32</td>
<td>Double-blind, placebo-controlled, n=39</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Primary endpoint</td>
</tr>
<tr>
<td>• Safety</td>
<td>• Percent change in urinary oxalate excretion from baseline through month 6</td>
</tr>
<tr>
<td><strong>STUDY 002</strong></td>
<td><strong>ILLUMINATE-B</strong></td>
</tr>
<tr>
<td>PH1 patients</td>
<td>PH1 patients</td>
</tr>
<tr>
<td>OLE n=20</td>
<td>Single-arm, open-label n=18</td>
</tr>
<tr>
<td>Up to 54 months’ dosing</td>
<td>Primary endpoint</td>
</tr>
<tr>
<td>• eGFR ≥45 mL/min/1.73 m²</td>
<td>• eGFR ≥30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>• 6-64 years old</td>
<td>• ≥6 years old</td>
</tr>
<tr>
<td>• Up to 3 doses</td>
<td>• eGFR ≥45 mL/min/1.73 m² if ≥12 months old</td>
</tr>
<tr>
<td><strong>EXTENSION PERIOD</strong></td>
<td><strong>ILLUMINATE-C</strong></td>
</tr>
<tr>
<td>PH1 patients</td>
<td>PH1 patients</td>
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<tr>
<td>Up to 54 months’ dosing</td>
<td>Up to 54 months’ dosing</td>
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<tr>
<td><strong>EXTENSION PERIOD</strong></td>
<td><strong>EXTENSION PERIOD</strong></td>
</tr>
<tr>
<td>Up to 54 months’ dosing</td>
<td>Up to 54 months’ dosing</td>
</tr>
</tbody>
</table>

**Clinical pharmacology study**
- Efficacy and safety studies in patients with PH1

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- Normal serum creatinine if <12 months old.
- Elevated serum creatinine if <12 months old
- eGFR, estimated glomerular filtration rate; hr, hour; min, minute; OLE, open-label extension; PH1, primary hyperoxaluria type 1

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Urinary Oxalate Assays Used in Clinical Trials of Lumasiran

- Enzymatic assay used in the Phase 1/2 study
  - Used clinically for diagnosis and clinical management
  - Available at multiple clinical labs

- Validated LC-MS/MS assay used in all Phase 3 studies
  - Developed by Alnylam to meet FDA and EMA regulatory requirements
  - Assay range: 5.00–250 µg/mL (0.0555–2.78 mmol/L)

- Pearson correlation between the two methods is 0.925

- LC-MS/MS assay values are higher than those of enzymatic assay; however, Phase 2 OLE 24 hr urinary oxalate percent reduction is consistent between the two
ILLUMINATE-A Phase 3 Study Design

PATIENT POPULATION (N=39)

- Adults and children ≥6 years
- Urinary oxalate excretion ≥0.7 mmol/24 hr/1.73 m²
- Confirmed AGXT mutations
- eGFR ≥30 mL/min/1.73 m²

6-MONTH DOUBLE-BLIND TREATMENT PERIOD

- Lumasiran qM × 3 loading dose, then q3M³
  3.0 mg/kg subcutaneously

- Placebo qM × 3 loading dose, then q3M subcutaneously

54-MONTH EXTENSION PERIOD

- Lumasiran q3M
  3.0 mg/kg subcutaneously

- Treatment arms were stratified at randomization based upon mean 24 hr urinary oxalate from the first 2 valid samples collected during screening (≤1.70 mmol/24 hr/1.73 m² vs >1.70 mmol/24 hr/1.73 m²)
- Oxalate was measured with a validated liquid chromatography-tandem mass spectrometry assay

NOTE:

³Maintenance dose of 3.0 mg/kg (q3M) starts 1 month after last loading dose. ⁴Patients randomized to placebo receive loading doses of 3.0 mg/kg lumasiran at months 6, 7, and 8; patients randomized to lumasiran receive a maintenance dose of 3.0 mg/kg lumasiran at month 6, and placebo at months 7 and 8

AGXT, alanine-glyoxylate aminotransferase gene; eGFR, estimated glomerular filtration rate; hr, hour; min, minute; q3M, once every 3 months; qM, once monthly; qM × 3, once monthly for 3 consecutive months
1 patient discontinued study drug after receiving 1 dose and subsequently withdrew from study due to inability to comply with protocol

1 patient discontinued treatment due to AE (fatigue and disturbance in attention), but completed study assessments through month 6 and remains in safety follow-up
ILLUMINATE-A: Baseline Demographic Characteristics
Balanced between placebo and lumasiran groups

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Placebo (N=13)</th>
<th>Lumasiran (N=26)</th>
<th>Overall (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at informed consent, years (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric (0–18 years), n (%)</td>
<td>17.0 (6–60)</td>
<td>18.7 (6–47)</td>
<td>18.1 (6–60)</td>
</tr>
<tr>
<td></td>
<td>8 (61.5)</td>
<td>14 (53.8)</td>
<td>22 (56.4)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>8 (61.5)</td>
<td>18 (69.2)</td>
<td>26 (66.7)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9 (69.2)</td>
<td>21 (80.8)</td>
<td>30 (76.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (23.1)</td>
<td>3 (11.5)</td>
<td>6 (15.4)</td>
</tr>
<tr>
<td>Other or &gt;1 race</td>
<td>1 (7.7)</td>
<td>2 (7.7)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>8 (61.5)</td>
<td>10 (38.5)</td>
<td>18 (46.2)</td>
</tr>
<tr>
<td>North America</td>
<td>2 (15.4)</td>
<td>11 (42.3)</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td>Middle East</td>
<td>3 (23.1)</td>
<td>5 (19.2)</td>
<td>8 (20.5)</td>
</tr>
</tbody>
</table>
## ILLUMINATE-A: Baseline Clinical Characteristics
Balanced between placebo and lumasiran groups

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Placebo (N=13)</th>
<th>Lumasiran (N=26)</th>
<th>Overall (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24 hr urinary oxalate excretion corrected for BSA&lt;sup&gt;a&lt;/sup&gt; (SD), mmol/24 hr/1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.79 ± 0.68</td>
<td>1.84 ± 0.60</td>
<td>1.82 ± 0.62</td>
</tr>
<tr>
<td>Mean 24 hr urinary oxalate:creatinine ratio&lt;sup&gt;b&lt;/sup&gt; (SD), mmol/mmol</td>
<td>0.237 ± 0.110</td>
<td>0.209 ± 0.101</td>
<td>0.218 ± 0.104</td>
</tr>
<tr>
<td>Mean plasma oxalate&lt;sup&gt;c&lt;/sup&gt; (SD), µmol/liter</td>
<td>15.5 ± 7.3</td>
<td>14.8 ± 7.6</td>
<td>15.0 ± 7.4</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall, mean (SD)</td>
<td>78.9 ± 26.8</td>
<td>83.0 ± 25.5</td>
<td>81.6 ± 25.7</td>
</tr>
<tr>
<td>≥90 (CKD stage 1), n (%)</td>
<td>4 (30.8)</td>
<td>9 (34.6)</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td>60–&lt;90 (CKD stage 2), n (%)</td>
<td>6 (46.2)</td>
<td>13 (50.0)</td>
<td>19 (48.7)</td>
</tr>
<tr>
<td>45–&lt;60 (CKD stage 3a), n (%)</td>
<td>1 (7.7)</td>
<td>2 (7.7)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>30–&lt;45 (CKD stage 3b), n (%)</td>
<td>2 (15.4)</td>
<td>2 (7.7)</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>Pyridoxine (vitamin B6) use, n (%)</td>
<td>9 (69.2)</td>
<td>13 (50.0)</td>
<td>22 (56.4)</td>
</tr>
<tr>
<td>Nephrocalcinosis grade ≥1, n (%)</td>
<td>12 (92.3)</td>
<td>17 (70.8)</td>
<td>29 (78.4)</td>
</tr>
<tr>
<td>Number of patients with reported history of symptomatic renal stone events&lt;sup&gt;e&lt;/sup&gt;, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime</td>
<td>10 (76.9)</td>
<td>23 (88.5)</td>
<td>33 (84.6)</td>
</tr>
<tr>
<td>12 months prior to consent</td>
<td>4 (30.8)</td>
<td>11 (42.3)</td>
<td>15 (38.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup>ULN is 0.514 mmol/24 hr/1.73 m<sup>2</sup>. <sup>b</sup>ULN is 0.0799 mmol/mmol. <sup>c</sup>ULN is 12.11 µmol/liter. <sup>d</sup>Denominator includes all patients who had a graded renal ultrasound at baseline. <sup>e</sup>A renal stone event is defined as an event that includes at least one of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, or macroscopic hematuria due to a renal stone. BSA, body surface area; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; hr, hour; SD, standard deviation; ULN, upper limit of normal.
# Primary and Secondary Endpoints

ILLUMINATE-A met its primary endpoint and all tested secondary endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (N=13)</th>
<th>Lumasiran (N=26)</th>
<th>Difference, Lumasiran–Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent change in 24 hr urinary oxalate excretion corrected for BSA from baseline to month 6 (average of months 3 to 6)</td>
<td>10.8</td>
<td>65.4</td>
<td>53.5</td>
<td>1.7 × 10⁻¹⁴</td>
</tr>
<tr>
<td>Absolute change in 24 hr urinary oxalate corrected for BSA from baseline to month 6 (95% CI), mmol/24 hr/1.73 m²</td>
<td>−0.27</td>
<td>1.24</td>
<td>−0.98</td>
<td>1.2 × 10⁻¹¹</td>
</tr>
<tr>
<td>Percent change in 24 hr urinary oxalate:creatinine ratio from baseline to month 6 (95% CI)</td>
<td>−10.8</td>
<td>62.5</td>
<td>51.8</td>
<td>5.0 × 10⁻¹⁰</td>
</tr>
<tr>
<td>Percent change in plasma oxalate from baseline to month 6 (95% CI)</td>
<td>−0.3</td>
<td>39.8</td>
<td>39.5</td>
<td>2.9 × 10⁻⁸</td>
</tr>
<tr>
<td>Proportion of patients with 24 hr urinary oxalate level at or below 1.5 × ULN at month 6 (95% CI)</td>
<td>0.00</td>
<td>0.84</td>
<td>0.84</td>
<td>8.3 × 10⁻⁷</td>
</tr>
<tr>
<td>Proportion of patients with 24 hr urinary oxalate level at or below ULN at month 6 (95% CI)</td>
<td>0.00</td>
<td>0.52</td>
<td>0.52</td>
<td>0.0010</td>
</tr>
<tr>
<td>Absolute change in plasma oxalate from baseline to month 6 (95% CI), μmol/liter</td>
<td>1.3</td>
<td>−7.5</td>
<td>−8.7</td>
<td>3.9 × 10⁻⁷</td>
</tr>
<tr>
<td>Change in eGFR from baseline to month 6 (SD), mL/min/1.73 m²</td>
<td>−0.1</td>
<td>−2.6</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

*Estimated by MMRM. *Based on the plasma oxalate analysis set, including patients who had a baseline plasma oxalate level ≥1.5 × LLOQ. *Analyzed using a Cochran–Mantel–Haenszel test. *As pre-specified, no statistical testing was performed. BSA, body surface area; CI, confidence interval; eGFR, estimated glomerular filtration rate; hr, hour; LLOQ, lower limit of quantification; MMRM, mixed-effect model repeated measures; SD, standard deviation; ULN, upper limit of normal.
Primary Endpoint: Percent Change in 24 hr Urinary Oxalate from Baseline to Month 6

Rapid and sustained reduction in 24 hr urinary oxalate levels

Difference in LS mean average M3–M6 (Lumasiran–Placebo): −53.5%; p-value: 1.7 × 10^{-14}

Mean maximal reduction: 76.0%

Data in graph are mean ± SEM of observed values
BL, baseline; BSA, body surface area; hr, hour; LS, least squares; M, month; SEM, standard error of the mean
Subgroup Analysis: Percent Change in 24 hr Urinary Oxalate from Baseline to Month 6

Consistent treatment effect across all subgroups, including baseline 24 hr urinary oxalate excretion, pyridoxine use, and eGFR

Subgroup

Overall (n=39)
Age at screening
6 to <12 years (n=16)
12 to <18 years (n=6)
≥18 years (n=17)
Sex
Male (n=26)
Female (n=13)
Race
White (n=30)
Non-white (n=9)
Baseline vitamin B6 use
Yes (n=22)
No (n=17)
Baseline 24-hr urinary oxalate corrected for BSA
≤1.70 mmol/24 hr/1.73 m² (n=18)
>1.70 mmol/24 hr/1.73 m² (n=21)
Baseline eGFR
<60 mL/min/1.73 m² (n=7)
≥60 mL/min/1.73 m² (n=32)
History of symptomatic renal stone events in lifetime
Yes (n=33)
No (n=6)
Region analysis 1
North America (n=13)
Other (n=26)
Region analysis 2
Europe (n=18)
Other (n=21)

Percentage change from baseline in 24 hr oxalate corrected for BSA

Subgroup analysis was performed with a restricted maximum likelihood-based MMRM model and a forest plot was generated, showing the associated 95% CI of the treatment effect in urinary oxalate corrected for BSA. BSA, body surface area; CI, confidence interval; eGFR, estimated glomerular filtration rate; hr, hour; MMRM, mixed-effect model repeated measures.
Secondary Endpoint: Absolute Change in 24 hr Urinary Oxalate Levels from Baseline to Month 6

Rapid and sustained reduction in 24 hr urinary oxalate levels

Data in graph are mean ± SEM of observed values. ULN is 0.514 mmol/24 hr/1.73 m²
BL, baseline; BSA, body surface area; hr, hour; LS, least squares; M, month; SEM, standard error of the mean; ULN, upper limit of normal

Difference in LS mean average M3–M6 (Lumasiran–Placebo): −0.98 mmol/24 hr/1.73 m²; p-value: 1.2 × 10⁻¹¹
Secondary Endpoint: Percent Change in 24 hr Urinary Oxalate:Creatinine Ratio from Baseline to Month 6

Rapid and sustained reduction in 24 hr urinary oxalate:creatinine ratio

Data in graph are mean ± SEM of observed values
BL, baseline; hr, hour; LS, least squares; M, month; SEM, standard error of the mean

Difference in LS mean average M3–M6 (Lumasiran–Placebo): −51.8%; p-value: 5.0 × 10⁻¹⁰
Secondary Endpoints: Proportion of Patients with 24 hr Urinary Oxalate Level ≤1.5 × ULN or ≤ULN at Month 6

Majority of patients achieved near normalization (≤1.5 × ULN) or normalization (≤ULN) in 24 hr urinary oxalate levels at month 6

- Near normalization: Lumasiran, 84% vs. Placebo, 0%, p=8.3 × 10^{-7}
- Normalization: Lumasiran, 52% vs. Placebo, 0%, p=0.0010

*p-value is based on Cochran–Mantel–Haenszel test stratified by baseline 24 hr urinary oxalate corrected for BSA (≤1.7 vs >1.7 mmol/24 hr/1.73 m²)
BSA, body surface area; hr, hour; ULN, upper limit of normal
Secondary Endpoint: Percent Change in Plasma Oxalate from Baseline to Month 6

Rapid and sustained reduction in plasma oxalate levels

The plasma oxalate analysis set was defined as those patients who had a baseline plasma oxalate level ≥1.5 × LLOQ (LLOQ is 5.55 µmol/liter). Data in graph are mean ± SEM of observed values.

Difference in LS mean average M3–M6 (Lumasiran–Placebo): −39.5%; p-value: 2.9 × 10⁻⁸
Secondary Endpoint: Absolute Change in Plasma Oxalate from Baseline to Month 6

Rapid and sustained reduction in plasma oxalate levels

Data in graph are mean ± SEM of observed values. ULN is 12.11 µmol/liter. The plasma oxalate analysis set was defined as those patients who had a baseline plasma oxalate level ≥1.5 × LLOQ (LLOQ is 5.55 µmol/liter)

<table>
<thead>
<tr>
<th>Study visit</th>
<th>Patients (N)</th>
<th>Dosing</th>
<th>Patients (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>23</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>M1</td>
<td>17</td>
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<tr>
<td>M2</td>
<td>19</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>M3</td>
<td>21</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>M4</td>
<td>21</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>M5</td>
<td>21</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>M6</td>
<td>22</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

LS mean average of M3–M6 (µmol/liter)

- 1.3 Placebo (N=10)
- -7.5 Lumasiran (N=23)

Difference in LS mean average M3–M6 (Lumasiran–Placebo): -8.7 µmol/liter; p-value: 3.9 × 10⁻⁷
Secondary Endpoint: Change in eGFR from Baseline to Month 6

eGFR remained stable from baseline to month 6

Data in graph are mean ± SEM of observed values
BL, baseline; eGFR, estimated glomerular filtration rate; M, month; SEM, standard error of the mean; W, week
Exploratory Endpoints: Renal Stone Events and Nephrocalcinosis

No apparent difference between treatment groups with regard to renal stone events; 3 patients with improvements in nephrocalcinosis

Renal stone events\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=13)</th>
<th>Lumasiran (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASELINE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with reported history of symptomatic renal stone events, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime</td>
<td>10 (76.9)</td>
<td>23 (88.5)</td>
</tr>
<tr>
<td>12 months prior to consent</td>
<td>4 (30.8)</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td><strong>TREATMENT PERIOD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with post-baseline renal stone events, n (%)</td>
<td>2 (15.4)</td>
<td>5 (19.2)</td>
</tr>
</tbody>
</table>

Nephrocalcinosis\textsuperscript{b}

<table>
<thead>
<tr>
<th>Change from baseline to month 6</th>
<th>Placebo (N=12)</th>
<th>Lumasiran (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral improvement (1 grade)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Bilateral improvement (\geq1 grade)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Unilateral worsening (1 grade)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No change</td>
<td>11</td>
<td>19</td>
</tr>
</tbody>
</table>

\textsuperscript{a}A renal stone event was defined as an event that includes at least one of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, or macroscopic hematuria due to a renal stone. \textsuperscript{b}In the subset of patients with renal ultrasounds at baseline and month 6
Exploratory Endpoint: Change in Plasma Glycolate from Baseline to Month 6

Plasma glycolate initially increased and then plateaued, consistent with reduction in hepatic GO activity.

Data in graph are mean ± SEM of observed values.

BL, baseline; GO, glycolate oxidase; M, month; SEM, standard error of the mean.
Lumasiran Safety Profile

- There were no deaths, severe, or serious AEs
- All AEs were mild or moderate in severity
- Most common related AEs were injection-site reactions
  - All were transient and mild in severity, with no treatment interruption or discontinuation
  - Most common symptoms were erythema, pain, pruritus, or discomfort at the injection site
- No hepatic AEs reported in either group
- No clinically relevant changes in laboratory measures, vital signs, and electrocardiograms related to lumasiran were observed

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo (N=13)</th>
<th>Lumasiran (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>9 (69)</td>
<td>22 (85)</td>
</tr>
<tr>
<td>AEs occurring in ≥10% of patients in either group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-site reactions(^a)</td>
<td>0</td>
<td>9 (35)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (23)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2 (15)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>2 (15)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>AE leading to discontinuation of study treatment(^b)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>AE leading to study withdrawal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe AE</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Includes injection-site reactions, injection-site erythema, and injection-site pain. \(^b\)Fatigue and disturbance in attention

AE, adverse event
Conclusions

• PH1 is a rare devastating disease, with high morbidity and mortality in all age groups

• Current management options for PH1 are limited and there is an urgent need for new therapies that can reduce hepatic oxalate production, the key toxic metabolite in PH1

• Substantial reduction in urinary oxalate is expected to confer clinical benefit in patients with PH1

• ILLUMINATE-A is the first Phase 3, randomized, double-blind, placebo-controlled study, designed to evaluate safety and efficacy of lumasiran, an RNAi therapeutic, in the treatment of PH1

• Lumasiran reduced urinary oxalate, the cause of progressive renal failure in PH1, with the majority of patients achieving normal or near-normal levels within 6 months of treatment initiation; lumasiran also led to a substantial reduction in plasma oxalate

• Lumasiran had an encouraging safety profile
  – Most common drug-related AEs were injection-site reactions, all of which were mild and transient
  – No severe or serious AEs reported
Thank you to the patients, investigators, and study staff who participated in the ILLUMINATE-A study

ILLUMINATE-A study collaborators:

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- Stephen Benedict Walsh
- Jenny Weinbrand-Goichberg
- Irith Weissman
- Karla Zepeda

The authors thank Sofia Fountana, PhD of Adelphi Communications, Bollington, UK for providing medical writing support, which was funded by Alnylam Pharmaceuticals Inc., Cambridge, MA, US in accordance with Good Publication Practice (GPP3) guidelines.
To those who say “impossible, impractical, unrealistic,” we say:

CHALLENGE ACCEPTED