SAFETY AND EFFICACY OF LUMASIRAN, AN INVESTIGATIONAL RNA INTERFERENCE (RNAi) THERAPEUTIC, IN ADULT AND PEDIATRIC PATIENTS WITH PRIMARY HYPEROXALURIA TYPE 1

Interim Results of Ongoing Phase 2 OLE
April 14, 2019
Primary Hyperoxaluria Type 1 (PH1):

- 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: 1-3/1,000,000 in Europe\(^1\) and ~32/1,000,000 in Middle East\(^2\)

Pathophysiology\(^1\):

- Overproduction of oxalate results in insoluble calcium oxalate crystals leading to urolithiasis, nephrocalcinosis, and kidney failure
- Disease course ultimately leads to multi-organ damage from systemic oxalosis

No therapies are approved for treatment of PH1

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Lumasiran

Investigational RNAi Therapeutic for Primary Hyperoxaluria Type 1

Lumasiran (ALN-GO1):

- Subcutaneously-administered small interfering RNA (siRNA)
  - Harnesses natural RNA interference (RNAi) mechanism

Therapeutic Hypothesis:

- Lumasiran targets liver hydroxyacid oxidase 1 (HAO1) mRNA, decreasing production of glycolate oxidase (GO) and hence reduces hepatic oxalate production
**Lumasiran Phase 1/2 and Phase 2 OLE**

**Study Design**

Patients previously dosed in Phase 1/2† study eligible to enroll into Phase 2^ open-label extension (OLE) study

- All patients completed follow-up in Phase 1/2 have enrolled in OLE (N=20)
  - Data presented here represent 18 patients dosed in Phase 2 OLE, as of 8 Feb 2019
  - Preliminary efficacy data of urinary oxalate and urinary oxalate/creatinine ratio includes 9 and 10 patients, respectively, who have reached Day 85
- Patients have been on study for a median of 4 months (range: 0.03–8.36; N=18)

**Phase 1/2 Part B – Patients with PH1 (N=20)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mg/kg, q28d x 3 SC</td>
<td>8</td>
</tr>
<tr>
<td>3.0 mg/kg, q28d x 3 SC</td>
<td>8</td>
</tr>
<tr>
<td>3.0 mg/kg, q84d x 2 SC</td>
<td>4</td>
</tr>
</tbody>
</table>

**Phase 2 OLE (N=18)**

- Doses listed are the initial dose patients received in the Phase 2 OLE
- Patients were started at their original dose from the Phase 1/2 study unless different dose approved prior to dosing

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
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<tbody>
<tr>
<td>1.0 mg/kg, q28d SC</td>
<td>3</td>
</tr>
<tr>
<td>3.0 mg/kg, q28d SC</td>
<td>6</td>
</tr>
<tr>
<td>3.0 mg/kg, q84d SC</td>
<td>9</td>
</tr>
</tbody>
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**Washout period‡ (mean 279 days)**

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†ClinicalTrials.gov Identifier: NCT02706886; EudraCT Number: 2015-004407-23; \(^*\)ClinicalTrials.gov Identifier: NCT03350451; EudraCT Number: 2016-003134-24; \(^*\)Patients were required to be followed for at least 84 days after the last dose of study drug in Phase 1/2 and meet the eligibility criteria to enroll into Phase 2 OLE
Lumasirian Phase 1/2 Study Part B

Summary of Results

20 Patients Enrolled

- Multiple doses of lumasirian demonstrated an acceptable safety profile in patients with PH1 with no discontinuations from study or drug related SAEs
- Mean maximal reduction in urinary oxalate of 75% (range: 43-87%) relative to baseline after lumasirian dosing in all cohorts†
  - The mean reduction relative to baseline 28 days post last dose of lumasirian was 66%

Data cut-off: 15 Aug 2018; Only data points with at least 3 contributing patients are represented.
†Patients who completed the Study Day 85 visit and had a valid 24-hour urinary oxalate assessment; placebo data not shown due to limited valid collections
#Patients randomized to placebo received subsequent dosing of lumasirian and are included in the lumasirian dosing cohort in which they were randomized with day 1 relative to first dose of lumasirian; patient randomized to placebo in 3 mg/kg quarterly dosing only received a single dose of lumasirian on Day 1
PH1, primary hyperoxaluria type 1; SAE, serious adverse event; Frishberg Y et al. Pediatr Neprol. 2018 (Abstracts – 51st ESPN Meeting, Antalya, Tukey, October 2018)
## Phase 2 OLE Patient Demographics*

<table>
<thead>
<tr>
<th>Baseline Characteristics (from Phase 1/2)</th>
<th>Results (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>15.1 (6 – 43)</td>
</tr>
<tr>
<td>Age &lt;18 years</td>
<td>78%</td>
</tr>
<tr>
<td>Gender, females</td>
<td>67%</td>
</tr>
<tr>
<td>Mean weight, kg (range)</td>
<td>50.1 (21.3 – 110)</td>
</tr>
<tr>
<td>Mean eGFR, mL/min/1.73m² (range)</td>
<td>74 (42–131)</td>
</tr>
<tr>
<td>Mean Urine Oxalate Content, mmol/24hr/1.73m² (range)</td>
<td>1.66 (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>

*Data cut-off: 8 Feb 2019*
Lumasiran Phase 2 OLE*

Safety

Continued dosing with lumasiran was well tolerated in patients with PH1

- No discontinuations from study treatment

- A single patient (1/18; 5.6%) reported 2 SAEs (traumatic brain injury and bone contusion†); none assessed as related to study drug

- AEs reported in 12/18 (66.7%) of patients;
  - Majority of AEs were reported in single patients, were mild in severity and assessed as unrelated to study drug

- 3/18 (16.7%) patients reported injection site reactions; all were mild and assessed as related to study drug

- No clinically significant laboratory changes

*Data cut-off: 8 Feb 2019; †SAE of traumatic brain injury and contusion was sustained during a car accident
Lumasiran Phase 2 OLE*

Pharmacodynamics: Urinary Oxalate Content

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)†

The mean reduction relative to Phase 1/2 baseline at day 85 was 69% (N=7)

*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 2 OLE*

Pharmacodynamics: 24-hour Urine Oxalate/Creatinine Ratio

Mean maximal reduction in urinary oxalate/creatinine ratio of 77% (range: 57-91%) relative to Phase 1/2 baseline after lumasiran in all cohorts (N=10)†

The mean reduction relative to Phase 1/2 baseline at day 85 was 70% (N=9)

*Data cut-off: 8 Feb 2019; †Patients who have urine oxalate/creatinine ratio at or after Day 85; ‡Patients with urine oxalate/creatinine ratio performed in the Phase 1/2 study collected within 30 days before Day 1 were not required to repeat the assessment.
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 who have completed follow-up in Phase 1/2 have enrolled in ongoing Phase 2 OLE.

Multiple doses of lumasiran demonstrated an acceptable safety profile in patients with PH1 with no discontinuations from study treatment or drug-related SAEs.

Patients in Phase 2 OLE experienced clinically significant and sustained reductions in urinary oxalate.

Phase 3 ILLUMINATE-A† currently enrolling adults and children with PH1.
To those who say “impossible, impractical, unrealistic,” we say:

CHALLENGE ACCEPTED