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

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Background and Rationale

Primary Hyperoxaluria Type 1 (PH1):

Disease Background

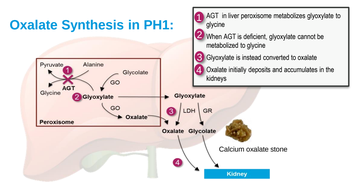
- Due to defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- Phenotype varies significantly in patients and may present at any age, typically in childhood
- Prevalence of PH1: 1-3/1,000,000 in Europe[1] and ~ 32/1,000,000 in Middle East[2]

Pathophysiology[1]

- 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

Oxalate Synthesis in PH1:



Lumasiran (ALN-GO1)[4]:

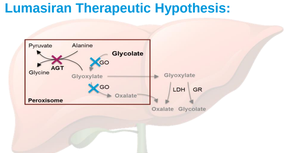
Subcutaneously-administered small interfering RNA (siRNA)

- 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 Therapeutic Hypothesis:



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

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)

- Data presented here represent 20 patients dosed in Phase 2 OLE, as of 12 Sep 2019
- All patients have been on study for a median of 10.4 months (range: 7 – 17; N=20)

Inclusion Criteria for Phase 2 OLE Study:

- Patients with PH1
- Ages 6-64 years
- eGFR > 45 ml/min/1.73m^2
- Urinary oxalate excretion ≥ 0.70 mmol/24h/1.73m^2
- Tolerated lumasiran in Phase 1/2 study

Initial Dosing in Phase 2 OLE (N=20)

- 1.0 mg/kg, monthly SC, N=3†
- 3.0 mg/kg, monthly SC, N=7
- 3.0 mg/kg, quarterly SC, N=10

†At time of data cut, all patients have transitioned to 3.0 mg/kg quarterly dosing

Results

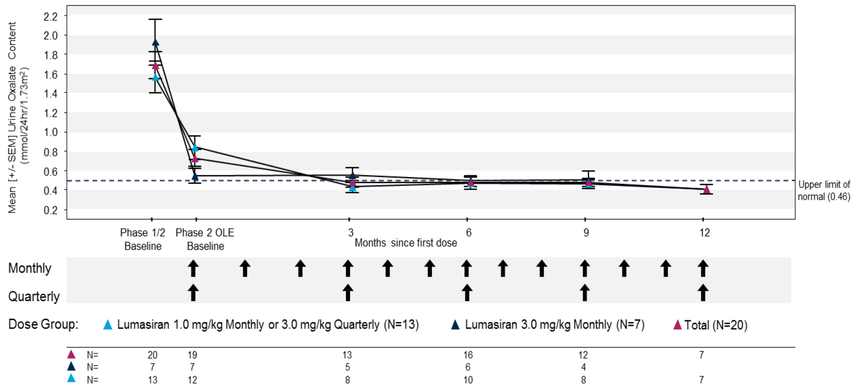
Phase 2 OLE Patient Demographics

Baseline Characteristics	Results (N=20)
Mean age, years (range)	16 (7 - 44)
Age <18 years	75%
Gender, females	65%
Mean weight, kg (range)	50.0 (21.3 – 112.5)
Mean eGFR, mL/min/1.73m^2 (range)	77 (42 – 131)
Mean Urine Oxalate Content, mmol/24hr/1.73m^2 (range)*	1.69 (0.83 – 2.97)
Mean 24-hour Urine Oxalate:Creatinine Ratio, mg/mg (range)*	0.17 (0.07 – 0.30)

Results Continued

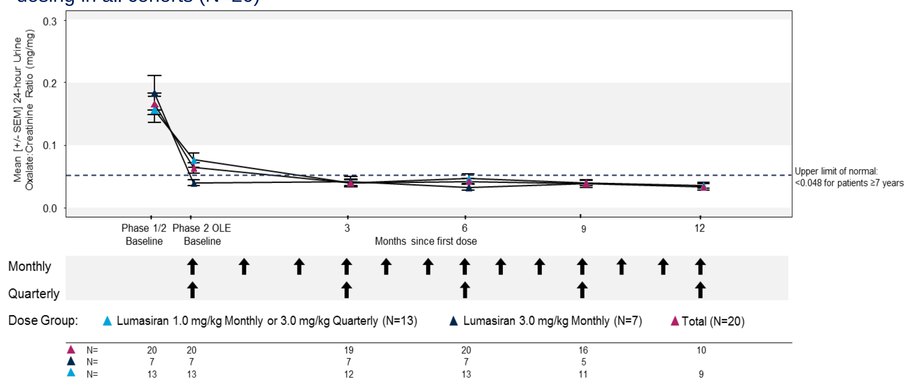
Urinary Oxalate Content in 24-hour urinary collections†

- Patients experienced sustained reductions in urinary oxalate content
- Mean maximal reduction in urinary oxalate of 76% (range: 43-91%) relative to Phase 1/2 baseline in all cohorts (N=19)‡
- 100% of patients achieved a urinary oxalate level ≤1.5x ULN and 68% of patients achieved a urinary oxalate level within normal range (N=19)^



Urinary 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)



Results Continued

Safety: Phase 2 OLE

Continued dosing with lumasiran was generally well tolerated in patients with PH1

- No discontinuations from study treatment
- A single patient (1/20; 5.0%) reported 2 SAEs (traumatic brain injury and bone contusion sustained during car accident); none assessed as related to study drug
- AEs reported in 19/20 (95%) of patients; majority were reported in single patients
  - AEs reported in more than 1 patient were: injection site reaction (n=4); headache, oropharyngeal pain (n=3); gastroenteritis, viral gastroenteritis, pyrexia, vomiting (n=2)
  - Majority of AEs were mild in severity and assessed as unrelated to study drug
- 4/20 (20%) patients reported injection site reactions; all were mild and assessed as related to study drug
- No clinically significant laboratory changes

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 SAEs
- 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

Data cut-off: 12 Sep 2019
*Baseline characteristics are derived from Phase 1/2 study
†Only data points with at least 3 contributing patients are represented
‡Patients who had a valid 24-hour urinary oxalate assessment
^1.5x ULN is defined as 0.69 mmoL/24hr/1.73m^2

References: 1. Cochat P, et al. *New Engl J Med.* 2013. 2. Abumwais JQ, et al. *Saudi J Kid Dis Transpl.* 2012. 3. Cochat P. *Kidney Int.* 1999. 4. Liebow A, et al. *J Am Soc Nephrol.* 2017.
Disclosures. Study sponsored by Alnylam.
AE, adverse event; eGFR, estimated glomerular filtration rate; OLE, open-label extension; PH1, primary hyperoxaluria type 1; RNAi, RNA interference; SAE, serious adverse event; ULN, upper limit of normal