Final Results from the Phase 1/2 Trial of Lumasiran and Program Updates

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Alnylam® PHARMACEUTICALS

Lumasiran

Investigational RNA interference Therapeutic for Primary Hyperoxaluria Type 1 (PH1)

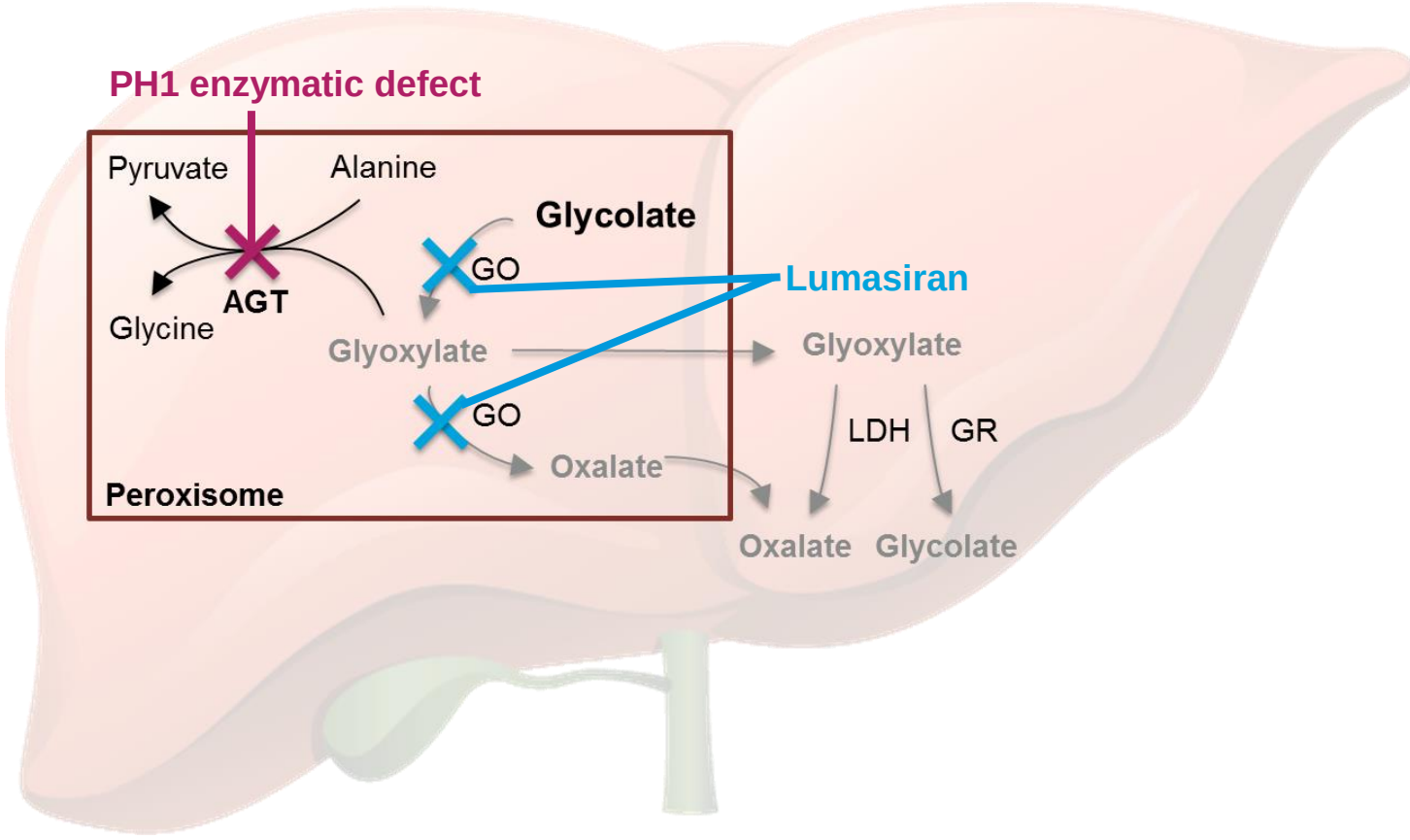
Lumasiran (ALN-GO1):

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

Therapeutic Hypothesis:

- Lumasiran targets the mRNA for *HAO1* which encodes glycolate oxidase (GO) in the liver; the decreased production of GO 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.

HAO1, hydroxyacid oxidase 1

Liebow A, et al. *J Am Soc Nephrol*. 2017.

Lumasiran Phase 1/2 Study†

Study Design & Demographics: Part B (Patients with PH1)

Multiple-Ascending Dose (MAD) | Randomized 3:1, Single-blind, Placebo-controlled

- 1.0 mg/kg, q28d x 3 SC, N=4
- 3.0 mg/kg, q28d x 3 SC, N=4
- 3.0 mg/kg, q84d x 2 SC, N=4

Patients randomized to placebo received subsequent dosing of lumasiran

Expansion Cohorts | Open-label

- 1.0 mg/kg, q28d x 3 SC, N=4
- 3.0 mg/kg, q28d x 3 SC, N=4

Inclusion Criteria:

- Patients with PH1
- Ages 6-64 years
- eGFR > 45 ml/min/1.73m^2
- Urinary oxalate excretion > 0.70 mmol/24h/1.73m^2

Key Endpoints:

- Safety and tolerability
- Urinary oxalate excretion
- Urinary oxalate to creatinine ratio

After median follow up of 9.8 months (range: 5.6 – 15.2), all patients enrolled in an open-label extension (OLE) study# for long-term dosing

†NCT02706886; #NCT03350451
eGFR, estimated glomerular filtration rate

Lumasiran Phase 1/2 Study

Patient Demographics: Part B (Patients with PH1)

Baseline Characteristics	Result (N=20)
Mean age, years (range)	14.9 (6–43)
Age <18 years	80%
Gender, females	65%
Mean weight, kg (range)	50.0 (21.3–112.5)
Mean eGFR, mL/min/1.73m^2 (range)	77.3 (42.5 –130.7)
Mean Urine Oxalate Content, mmol/24hr/1.73m^2 (range)	1.69 (0.83–2.97)
Mean 24-hour Urine Oxalate:Creatinine Ratio (range)	0.17 (0.07–0.30)

eGFR, estimated glomerular filtration rate

Lumasiran Phase 1/2 Study Results

Safety: Part B (Patients with PH1)

Multiple doses of lumasiran well tolerated in patients with PH1

- No discontinuations from study treatment
- SAEs reported in 1 (33%) patient during placebo dosing and 4 (20%) patients after lumasiran dosing; none considered related to study drug by investigator
  - Placebo: 1 patient with SAEs of acute pyelonephritis and kidney stones
  - Lumasiran: 1 patient with kidney stones; 1 patient with vomiting; 1 patient with gastroenteritis; and 1 patient with abdominal pain, fever and vomiting
- AEs reported in 2 (66.7%) patients during placebo dosing and 20 (100%) patients after lumasiran dosing
  - Majority of AEs were mild or moderate in severity and considered unrelated to study drug by investigator
  - Severe AEs reported: 1 (33%) patient during placebo dosing (acute pyelonephritis) and 1 (5%) patients after lumasiran dosing (kidney stone); none considered related to study drug by investigator
  - AEs reported in >3 patients receiving lumasiran: pyrexia (N=6); vomiting, cough, abdominal pain, headache (N=5 each); and rhinitis and nephrolithiasis (N=4 each)
  - Self-limiting injection site reactions (ISRs) reported in 3 (15%) patients receiving lumasiran; all mild or moderate and none affected dosing
- No clinically significant laboratory changes

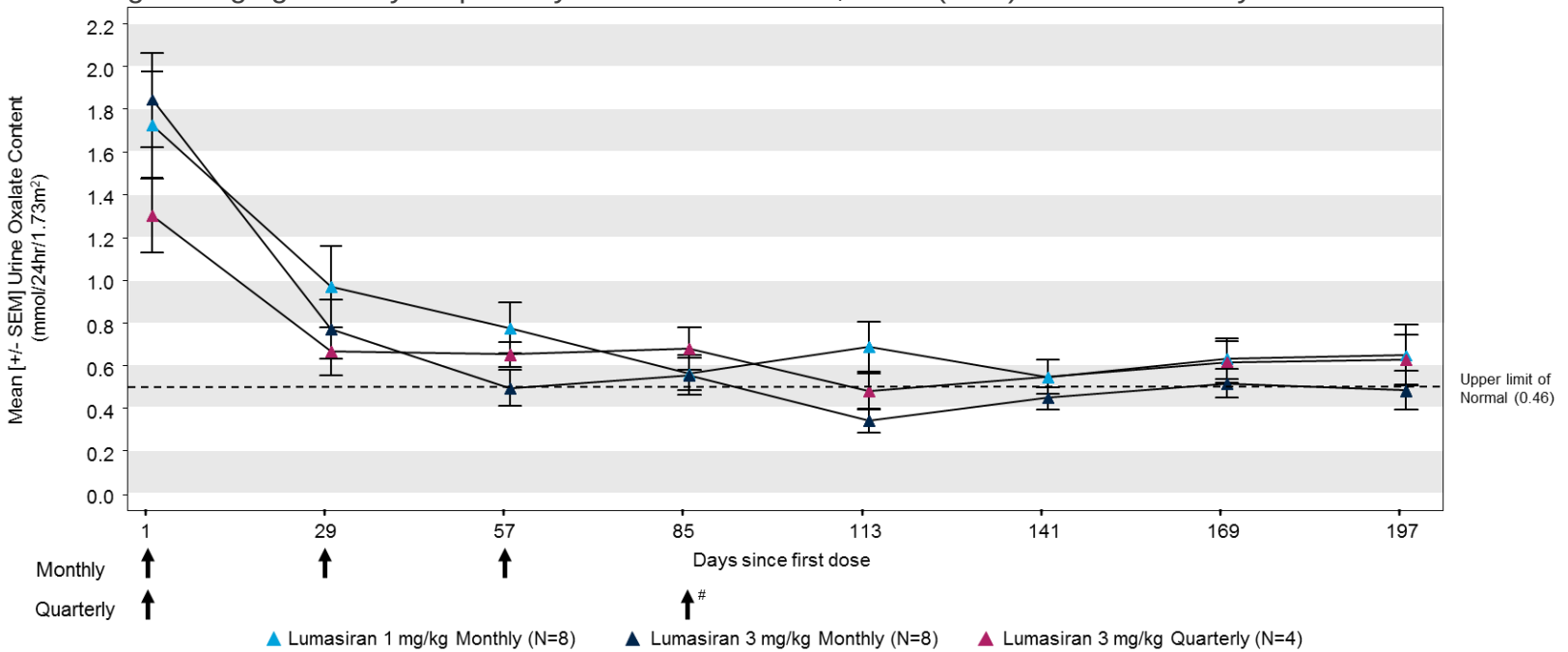
SAE, serious adverse event

Lumasiran Phase 1/2 Study Results

Pharmacodynamics: Urinary Oxalate Content in Part B (Patients with PH1)

Mean maximal reduction in urinary oxalate of 75% (range: 43-92%) relative to baseline after lumasiran dosing in all cohorts† (N=20)

- The mean reduction relative to baseline 28 days post last dose of lumasiran was 66%
- 100% of patients achieved a urinary oxalate level ≤1.5x ULN and 70% of patients achieved a urinary oxalate level within the normal range‡
  - Among patients receiving 3.0 mg/kg monthly or quarterly doses of lumasiran, 11/12 (92%) achieved urinary oxalate levels within the normal range

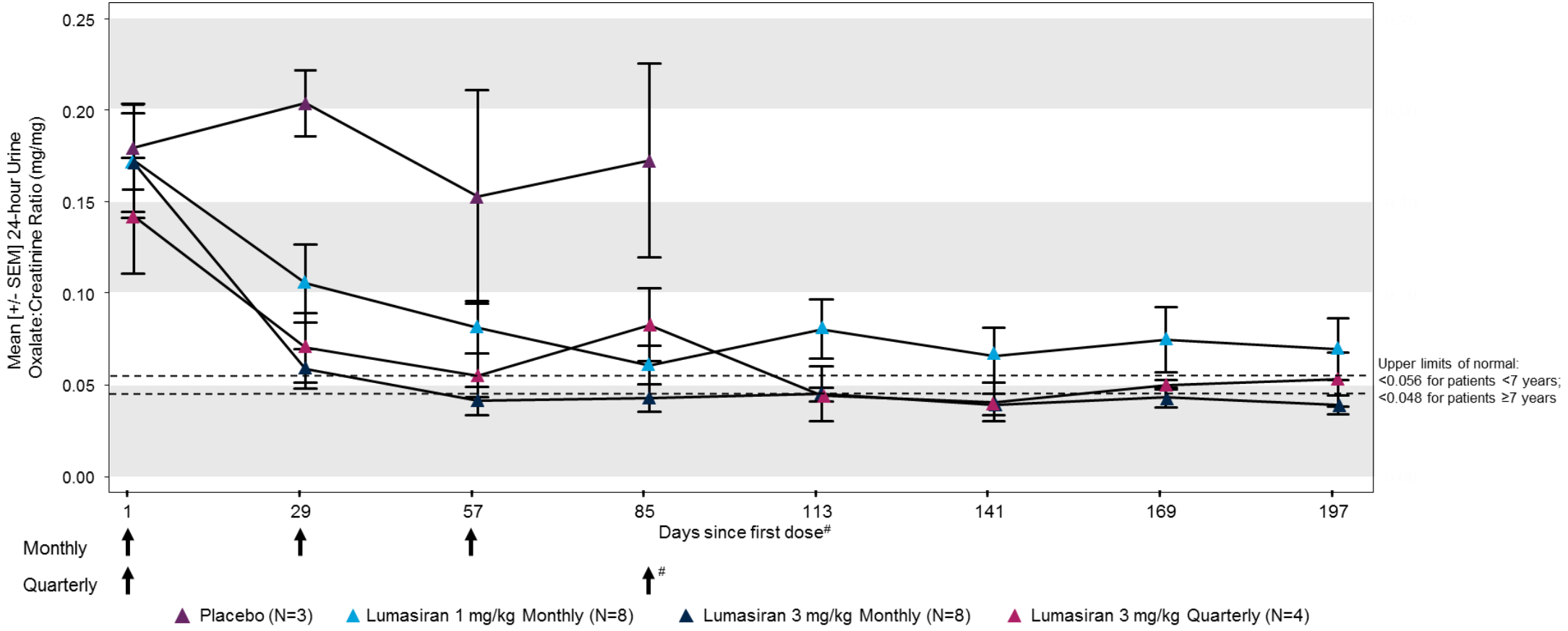


Only data points with at least 3 contributing patients are represented.
†Patients who had a valid 24-hour urinary oxalate assessment; placebo data not shown due to limited valid collections
‡1.5x ULN is defined as 0.69 mmol/24hr/1.73m^2; normal range is defined as ≤0.46 mmol/24hr/1.72m^2
#Patients randomized to placebo received subsequent dosing of lumasiran and are included in the lumasiran dosing cohort in which they were randomized with day 1 relative to first dose of lumasiran; patient randomized to placebo in 3 mg/kg quarterly dosing only received a single dose of lumasiran on Day 1
ULN, upper limit of normal

Lumasiran Phase 1/2 Study Results

Pharmacodynamics: Urinary Oxalate:Creatinine Ratio in Part B (Patients with PH1)

Mean maximal reduction in urinary oxalate:creatinine ratio of 77% (range: 50-95%) after lumasiran dosing in all cohorts (N=20)



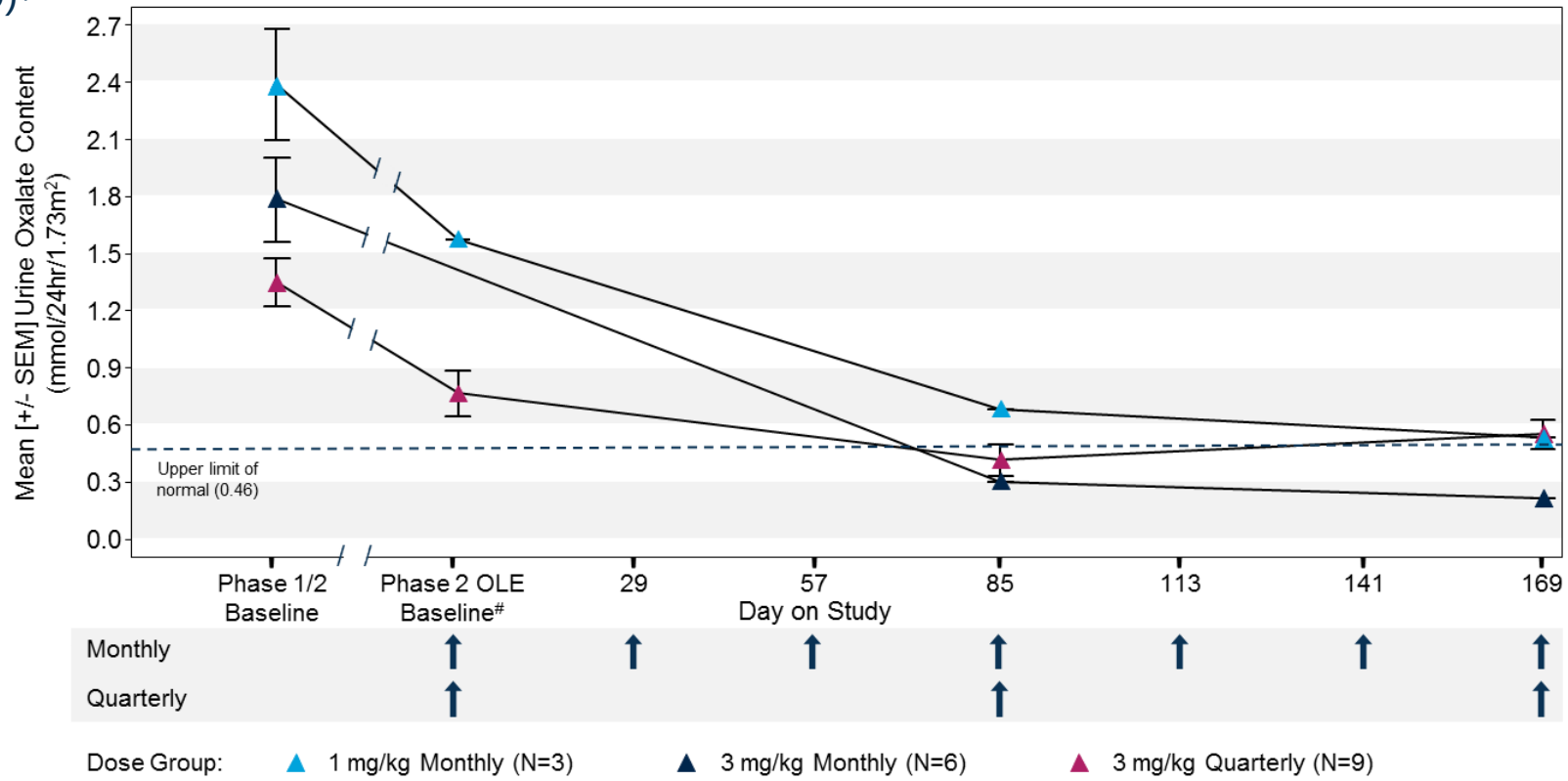
#Patients randomized to placebo received subsequent dosing of lumasiran and are included in the lumasiran dosing cohort in which they were randomized with Day 1 relative to first dose of lumasiran; patient randomized to placebo in 3 mg/kg quarterly dosing only received a single dose of lumasiran on Day 1

Lumasiran Phase 2 OLE Study

Summary of Initial Results*

As of February 2019, patients have been on OLE for a median of 4 months (range: 0.03–8.36; N=18)

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



*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 1/2 Study Results

Summary and Next Steps

Lumasiran (ALN-GO1) is a subcutaneously administered investigational RNAi therapeutic specifically designed to reduce hepatic production of oxalate in patients with PH1

Adult and pediatric patients receiving lumasiran experienced clinically significant and sustained reductions in urinary oxalate to normal or near normal levels

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

Data support the therapeutic hypothesis and the continued development of lumasiran across a spectrum of patients with PH1 in the Phase 3 ILLUMINATE[#] trials

ILLUMINATE

RNAi, RNA interference; SAE, serious adverse event
[#]NCT03681184; NCT03905694

ILLUMINATE-A*

A Phase 3 Study to Evaluate the Efficacy and Safety of Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1

Enrollment Complete

Patient population (N=30)

Key Inclusion Criteria:

- Adults and children ≥6 years
- Urinary oxalate excretion ≥0.7 mmol/24 h/1.73 m^2
- Confirmed alanine glyoxylate aminotransferase (*AGXT*) mutations
- eGFR >30 mL/min/1.73 m^2

2:1 Randomization

6-Month Double-Blind Treatment Period

Lumasiran
Three monthly loading doses then maintenance dose of 3.0 mg/kg†

Placebo
Equivalent volume for 3 monthly loading doses then maintenance dose

54-Month Extension Period

Lumasiran
3.0 mg/kg every 3 months

Primary Analysis at 6 Months:

- **Primary Endpoint:** Percent change in urinary oxalate excretion from baseline (average percent change from baseline across months 3 through 6)
- **Secondary Endpoints:** Change in 24-hour urinary oxalate:creatinine ratio; proportion of patients with 24-hour urinary oxalate level below ULN and 1.5 x ULN; change in eGFR; change in plasma oxalate

Top line results from this study expected in late 2019

*NCT03681184; EudraCT Number: 2018-001981-40
†3.0 mg/kg once monthly for 3 consecutive months (monthly for 3 doses: loading dose phase) followed by 3.0 mg/kg once every 3 months (maintenance phase) starting 1 month after the last loading dose.
eGFR, estimated glomerular filtration rate; Month, 28 days; PH1, primary hyperoxaluria type 1; ULN, upper limit of normal

ILLUMINATE-B*

A Phase 3 Study to Evaluate the Efficacy and Safety of Lumasiran in Young Children with Primary Hyperoxaluria Type 1

Now Enrolling

Patient population (N=8)

Key Inclusion Criteria:

- Infants and children <6 years
- Elevated urinary oxalate:creatinine ratio
- Confirmed alanine glyoxylate aminotransferase (*AGXT*) mutation
- eGFR >45 mL/min/1.73 m^2 if ≥12 months old; non-elevated serum creatinine if <12 months old

Open-Label

6-Month Open-Label Treatment Period

Lumasiran
Three monthly loading doses then maintenance dosing dependent on weight†

54-Month Open-Label Extension Period

Lumasiran
Continued once monthly or every 3 months maintenance dosing based on weight‡

Primary Analysis:

- **Primary Endpoint:** Percent change in urinary oxalate excretion at 6 months (average percent change from baseline across months 3 through 6)
- **Secondary Endpoints:** Percent change in urinary oxalate excretion (extension period); absolute change in urinary oxalate excretion; proportion of patients with 24-hour urinary oxalate level below ULN and 1.5xULN; plasma PK of lumasiran; change in eGFR

ILLUMINATE-C
to include patients with impaired renal function

*NCT03905694; EudraCT Number: 2018-004014-17
†Patients <10 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 3.0 mg/kg, Patients ≥10 kg to <20 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 6.0 mg/kg, Patients ≥20 kg: Three monthly loading doses at 3.0 mg/kg then maintenance dose of 3.0 mg/kg
‡Continued weight-based dosing using weight obtained 7 days prior to dosing
eGFR, estimated glomerular filtration rate; Month, 28 days; PH1, primary hyperoxaluria type 1; ULN, upper limit of normal

Acknowledgements

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