Lumasiran Lowered Urinary Oxalate in Patients With Primary Hyperoxaluria Type 1 Irrespective of Pyridoxine Use, Hydration Status, and Genotype in the Phase 3 Clinical Trial ILLUMINATE-A

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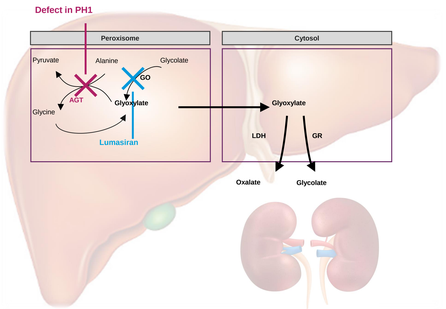
Conclusions

- **The Phase 3 ILLUMINATE-A trial demonstrated that lumasiran reduced urinary oxalate excretion, the cause of progressive kidney disease in PH1**
- **This subgroup analysis showed that the effect of lumasiran in reducing 24-hour urinary oxalate was consistent irrespective of patient baseline age, urinary oxalate levels, kidney function, use of concomitant pyridoxine, hydration status, crystallization inhibitor use, or *AGXT* genotype, and was sustained through Month 12**

Introduction

- Patients with PH1 overproduce oxalate due to a deficiency in the hepatic peroxisomal enzyme AGT[1,2] (**Figure 1**)
- Excess oxalate can lead to recurrent kidney stones, nephrocalcinosis, progressive kidney failure, and multiorgan damage from systemic oxalosis[1,2]
- Lumasiran is an RNAi therapeutic approved by the FDA for the treatment of PH1 to reduce urinary oxalate levels in pediatric and adult patients[3]
  - Lumasiran decreases hepatic oxalate production by inhibiting the production of GO[4] (**Figure 1**)
- In the Phase 3 ILLUMINATE-A trial (NCT03681184) involving patients with PH1 who were ≥6 years old with an eGFR ≥30 mL/min/1.73m^2, lumasiran reduced 24-hour urinary oxalate excretion by 53.5% relative to placebo (P=1.7x10^{-14}) during the 6-month double-blind treatment period[5]
  - The LS mean reduction from baseline was 65.4% in the lumasiran group and 11.8% in the placebo group[5]
- The subgroup analyses of ILLUMINATE-A presented here were performed to determine if baseline age, urinary oxalate excretion, eGFR, pyridoxine use, hyperhydration status, crystallization inhibitor use, and *AGXT* genotype impacted the treatment effect of lumasiran on 24-hour urinary oxalate excretion

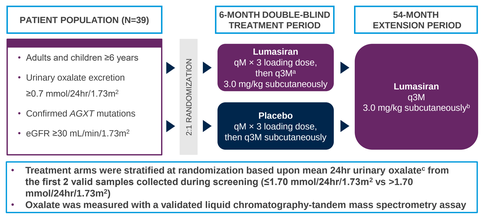
Figure 1. Defect in Glyoxylate Metabolism in Hepatocytes of Patients With Primary Hyperoxaluria Type 1 and Lumasiran Therapeutic Hypothesis



Methods

- ILLUMINATE-A is a randomized, double-blind, placebo-controlled, Phase 3 trial (**Figure 2**)

Figure 2. ILLUMINATE-A Phase 3 Study Design



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

[a]Maintenance dose of 3.0 mg/kg (q3M) started 1 month after last loading dose.
[b]Patients randomized to placebo received loading doses of 3.0 mg/kg lumasiran at Months 6, 7, and 8; patients randomized to lumasiran received a maintenance dose of 3.0 mg/kg lumasiran at Month 6, and placebo at Months 7 and 8.
[c]1.70 mmol/24hr/1.73m^2 = 153 mg/24hr/1.73m^2 (1 mmol/24hr/1.73m^2 = 90 mg/24hr/1.73m^2).
NCT03681184; EudraCT Number: 2018-001981-40.

- Patients taking pyridoxine (vitamin B6) were required to be on a stable regimen for at least 90 days before randomization
- All patients were to continue the PH1 standard of care regimen in place at the time of study enrollment, including hyperhydration, crystallization inhibitors, and/or pyridoxine therapy through Month 12
- Subgroup analyses were performed for percent reduction with lumasiran compared to placebo in 24-hour urinary oxalate from baseline to Month 6 (average of Months 3–6) in the following subgroups (N=39):
  - Baseline age (6 to <12, vs 12 to <18, vs ≥18 years), 24-hour urinary oxalate corrected for BSA (≤1.70 vs >1.70 mmol/24hr/1.73m^2), eGFR (<60 vs ≥60 mL/min/1.73m^2), pyridoxine use (yes vs no), hydration status, crystallization inhibitor use (yes vs no), and *AGXT* genotype
    - Baseline 24-hour urine volume was considered a surrogate for hydration status in this analysis: <1.5 L/m^2 (without hyperhydration) vs ≥1.5 L/m^2 (with hyperhydration)
    - *AGXT* genetic mutation subgroups were: M (missense)/M + M/N (nonsense); vs N/N; vs PR (pyridoxine-responsive) together with any other genotype (ie, PR/*)[6,7]
      - PR was defined as NM_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3(AGXT):c.454T>A (p.Phe152Ile)
  - The estimated treatment effect with lumasiran compared with placebo on percent change in 24-hour urinary oxalate in each subgroup was illustrated in a forest plot, with the LS mean, treatment difference in LS means, and 95% CIs derived using a mixed-effects model for repeated measures
- In addition, subgroup analyses of absolute change in 24-hour urinary oxalate from baseline to Month 12 in patients treated with lumasiran (N=26) were performed by baseline age, eGFR, pyridoxine use, hydration status, crystallization inhibitor use, and *AGXT* genotype
  - Descriptive statistics were generated for absolute change from baseline in 24-hour urinary oxalate subgroup analyses

Results

- A consistent treatment effect with lumasiran was observed across all prespecified subgroups, including baseline age, 24-hour urinary oxalate levels, kidney function (eGFR), and pyridoxine use, and across post-hoc subgroups, including baseline hydration status (baseline urine volume), crystallization inhibitor use, and *AGXT* genotype (**Figure 3**)

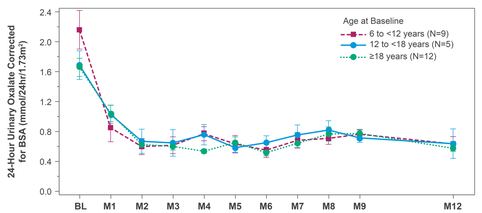
Figure 3. Forest Plot of Treatment Difference Between Lumasiran and Placebo in Percent Change in 24-hour Urinary Oxalate From Baseline to Month 6

Genotype: M, missense; N, nonsense; PR, pyridoxine-responsive. *Any genotype of PR, M, or N.

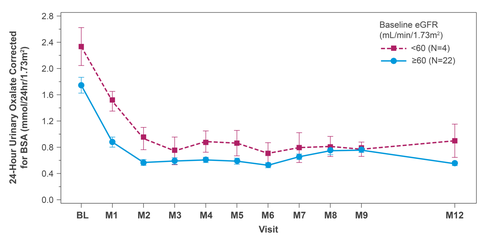
- Among the patients treated with lumasiran during the double-blind period (N=26) and continuing lumasiran in the extension period (N=24), absolute reduction in 24-hour urinary oxalate levels from baseline were sustained through Month 12 and were similar across patient subgroups, regardless of baseline age, kidney function, pyridoxine use, hydration status, crystallization inhibitor use, or *AGXT* genotype (**Figure 4**)

Figure 4. Absolute Values of 24-hour Urinary Oxalate Levels From Baseline to Month 12 in Patients Treated With Lumasiran by Baseline Characteristics

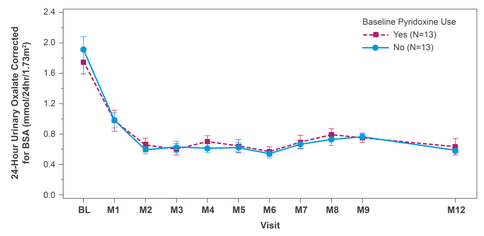
A. Age



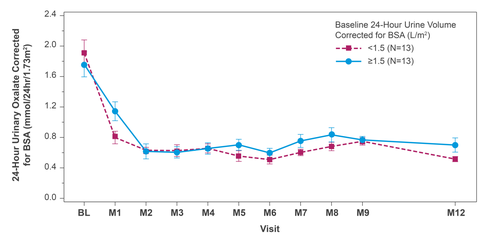
B. eGFR



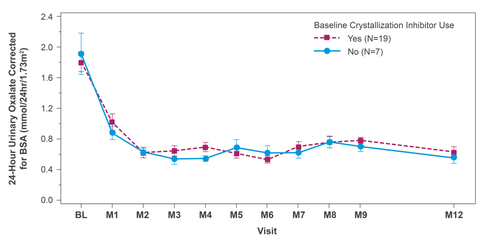
C. Pyridoxine Use



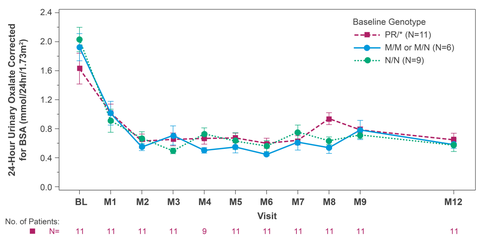
D. Hydration Status



E. Crystallization Inhibitor Use



F. *AGXT* Genotype



Data in graph are mean ± SEM of observed values.
Genotype: M, missense; N, nonsense; PR, pyridoxine-responsive. *Any genotype of PR, M, or N.

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Abbreviations: AGT, alanine-glyoxylate aminotransferase; BL, baseline; BSA, body surface area; CI, confidence interval; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; GO, glycolate oxidase; GR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; LS, least squares; M, month; PH1, primary hyperoxaluria type 1; q3M, once every 3 months; qM, once monthly; RNAi, ribonucleic acid interference; SEM, standard error of the mean.

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