LEADING EUROPEAN NEPHROLOGY

Deutsche Gesellschaft für Nephrologie

58TH ERA-EDTA CONGRESS FULLY VIRTUAL JUNE 5-8, 2021

Stable eGFR in Patients With Primary Hyperoxaluria Type 1 Treated With Lumasiran, Regardless of Kidney Function at Start of Treatment

Wesley Hayes[1], Sander F. Garrelfs[2], David J. Sas[3], John C. Lieske[4], Taylor Ngo[5], John M. Gansner[5], Tracy L. McGregor[5], Yaacov Frishberg[6]

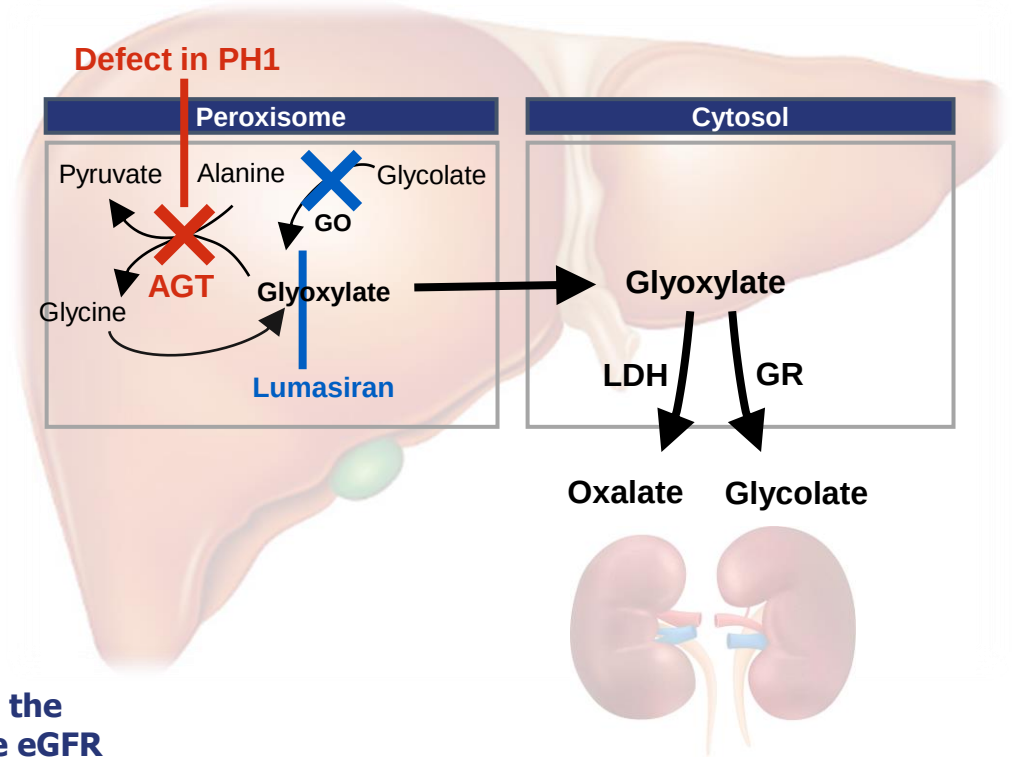
[1]Department of Paediatric Nephrology, Great Ormond Street Hospital, London, UK; [2]Department of Pediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [3]Division of Pediatric Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA; [4]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA; [5]Alnylam Pharmaceuticals, Cambridge, MA, USA; [6]Division of Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel

Disclosures

- **W Hayes:** travel and accommodation expenses from Alnylam Pharmaceuticals to attend an international investigators' meeting
- **SF Garrelfs:** non-financial support and grants from Alnylam Pharmaceuticals, and grants from Dicerna Pharmaceuticals
- **DJ Sas:** grants and other from Alnylam Pharmaceuticals and personal fees from Advicenne
- **JC Lieske:** grants from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, Retrophin, OxThera, and Siemens; other from Orfan-Bridgebio; and grants and other from Allena
- **T Ngo, JM Gansner, TL McGregor:** employees of Alnylam Pharmaceuticals
- **Y Frishberg:** consultancy fees from Alnylam Pharmaceuticals and membership in the safety review committee

Primary Hyperoxaluria Type 1 and Lumasiran

- PH1 is a rare genetic disorder characterized by hepatic oxalate overproduction due to a deficiency in the hepatic peroxisomal enzyme AGT[1,2]
- Approximately half of patients with PH1 progress to kidney failure by early adulthood, and nearly all by age 60 years[3,4]
- Lumasiran, a subcutaneously administered RNAi therapeutic approved for the treatment of PH1 in all age groups, decreases hepatic oxalate production by inhibiting the production of GO[5-7]
- In clinical trials, treatment with lumasiran resulted in substantial reductions in urinary and plasma oxalate in pediatric and adult patients, with an acceptable safety profile; eGFR remained stable with lumasiran treatment[8-11]



This analysis of pooled data from patients with PH1 and an eGFR of ≥30 mL/min/1.73m² enrolled in clinical trials of lumasiran evaluated the changes in kidney function in patient subgroups stratified by baseline eGFR

1. Cochat P, Rumsby G. *N Engl J Med.* 2013;369:649-58; 2. Milliner DS, et al. *GeneReviews®*. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1283; 3. Hopp K, et al. *J Am Soc Nephrol.* 2015;26:2559-70; 4. Harambat J, et al. *Kidney Int.* 2010;77:443-9; 5. OXLUMO (lumasiran) [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; 2020; 6. OXLUMO (lumasiran) [summary of product characteristics]. Alnylam Netherlands B.V.; 2020; 7. Liebow A, et al. *J Am Soc Nephrol.* 2017;28:494-503; 8. Frishberg Y, et al. *Clin J Am Soc Nephrol.* 2021; in press; 9. Garrelfs SF, et al. *N Engl J Med.* 2021;384:1216-26; 10. Saland J, et al. Presented at: Annual Meeting of the American Society of Nephrology; October 22-25, 2020; 11. Deschênes G, et al. Presented at: Annual Meeting of the American Society of Nephrology; October 22-25, 2020.
AGT, alanine-glyoxylate aminotransferase; eGFR, estimated glomerular filtration rate; GO, glycolate oxidase; GR, glyoxylate reductase/hydroxypyruvate reductase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1; RNAi, ribonucleic acid interference.

Pooled Analysis by Baseline eGFR Subgroup

- Data in this analysis were from 75 patients with PH1 (age ≥12 months[a]) enrolled in lumasiran studies; 46 were treated with lumasiran from the start of the study through the Month 12 visit

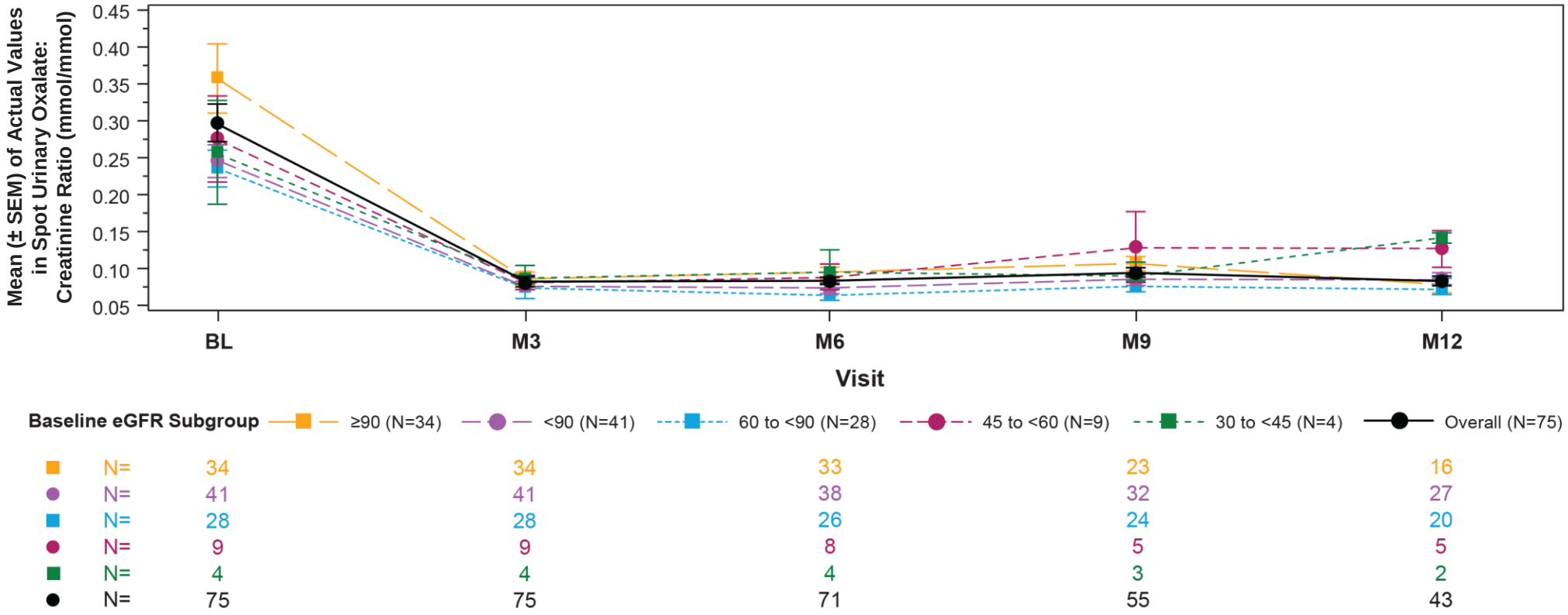
Study	Phase 2 Open-Label Extension (N=20)	Phase 3 ILLUMINATE-A (N=39)	Phase 3 ILLUMINATE-B (N=16)[a]
Study design	Long-term extension of Phase 1/2 study; up to 54 months of dosing	6-month, double-blind, placebo-controlled primary analysis period followed by a long-term extension period of up to 54 months	Single-arm, open-label study with a 6-month primary analysis period followed by a long-term extension period of up to 54 months
Patients	• Patients with PH1 who completed the Phase 1/2 study, part B • Age 6 to 64 years • eGFR >45 mL/min/1.73m^2	• Patients with PH1 • Age ≥6 years • eGFR ≥30 mL/min/1.73m^2	• Patients with PH1 • Age ≥12 months[a] to <6 years • eGFR >45 mL/min/1.73m^2

- eGFR calculated based on the Modification of Diet in Renal Disease Study equation for patients ≥18 years or the Schwartz Bedside equation for patients ≥12 months and <18 years[1,2]
- Baseline eGFR subgroups analyzed: ≥90, <90, 60 to <90, 45 to <60, and 30 to <45 mL/min/1.73m^2

Phase 2 open-label extension: NCT03350451. ILLUMINATE-A: NCT03681184; EudraCT Number: 2018-001981-40. ILLUMINATE-B: NCT03905694; EudraCT Number: 2018-004014-17.
[a]Two patients age <12 months from ILLUMINATE-B were excluded from the eGFR analysis, as the Schwartz Bedside equation is not validated for this age group.
1. Levey AS, et al. *Ann Intern Med.* 2009;150:604-12; 2. Schwartz GJ, et al. *J Am Soc Nephrol.* 2009;20:629-37.
eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1.

Spot Urinary Oxalate:Creatinine by eGFR Subgroup

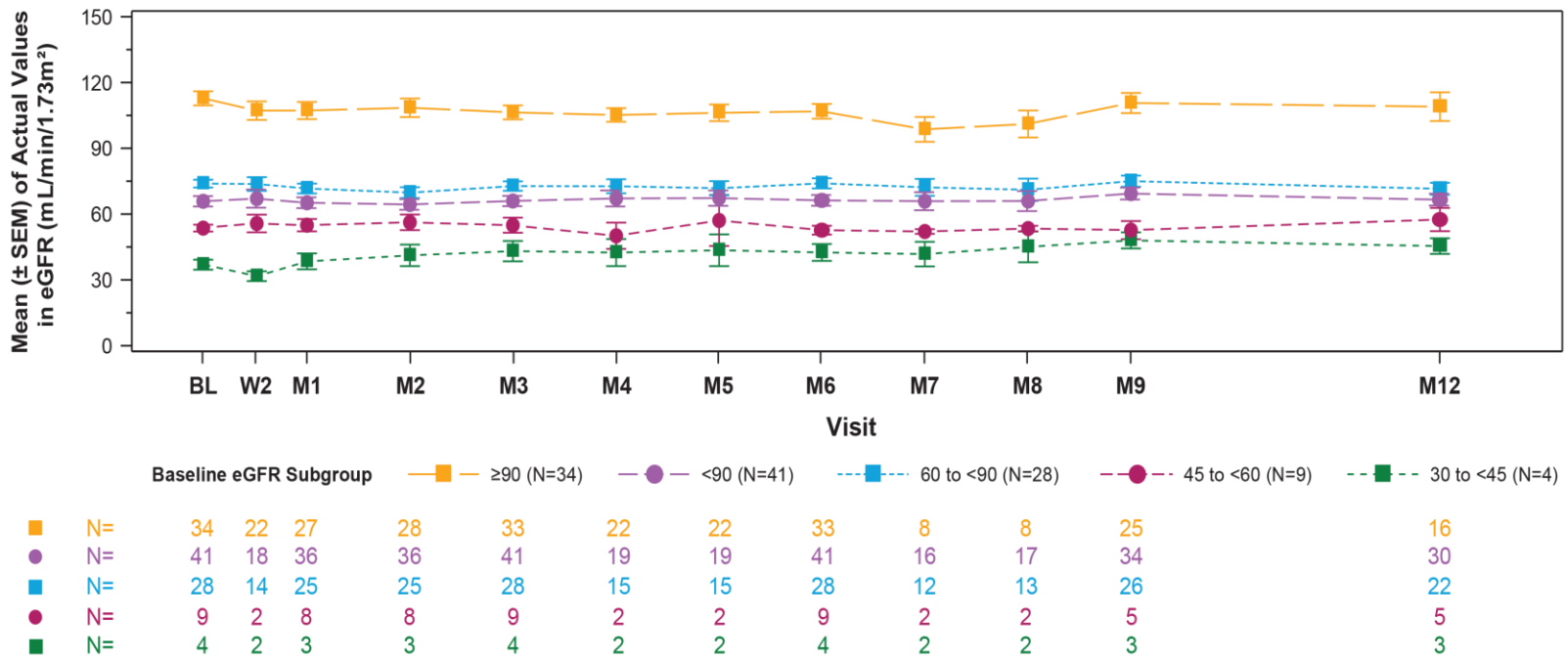
Treatment With Lumasiran Resulted in Substantial Reductions in Spot Urinary Oxalate: Creatinine Ratios, Regardless of Kidney Function at Baseline



BL, baseline; eGFR, estimated glomerular filtration rate; M, month; SEM, standard error of the mean.

eGFR Over Time by eGFR Subgroup

eGFR Remained Stable With Lumasiran Treatment Through Month 12 in All eGFR Subgroups



eGFR, mL/min/1.73m²	
Baseline eGFR subgroup	**Mean change (95% CI) from baseline to Month 12**
≥90 (N=16)	−1 (−8, 6)
<90 (N=30)	0 (−3, 3)
60 to <90 (N=22)	−2 (−5, 1)
45 to <60 (N=5)	3 (−8, 14)
30 to <45 (N=3)	9 (7, 11)

BL, baseline; eGFR, estimated glomerular filtration rate; M, month; SEM, standard error of the mean; W, week.

Conclusions

- Patients with PH1 had stable kidney function over time with lumasiran treatment, regardless of kidney function at baseline
- Given the progressive kidney function decline that is characteristic of PH1, the eGFR stability observed during 12 months of treatment with lumasiran is encouraging
- Treatment with lumasiran resulted in substantial reductions in urinary oxalate across patient subgroups with various degrees of kidney function impairment at baseline
- Kidney function will continue to be monitored for the duration of the lumasiran clinical trials

Acknowledgments

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the lumasiran clinical studies. This study was funded by Alnylam Pharmaceuticals. Medical writing and editorial assistance were provided by Peloton Advantage, LLC, an OPEN Health company, in accordance with Good Publication Practice (GPP3) guidelines, and funded by Alnylam Pharmaceuticals.

eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1.