Development of Lumasiran for the Treatment of Primary Hyperoxaluria Type 1

Pushkal P. Garg, MD; Chief Medical Officer, Alnylam Pharmaceuticals

Oligonucleotide Therapeutics Society Annual Meeting

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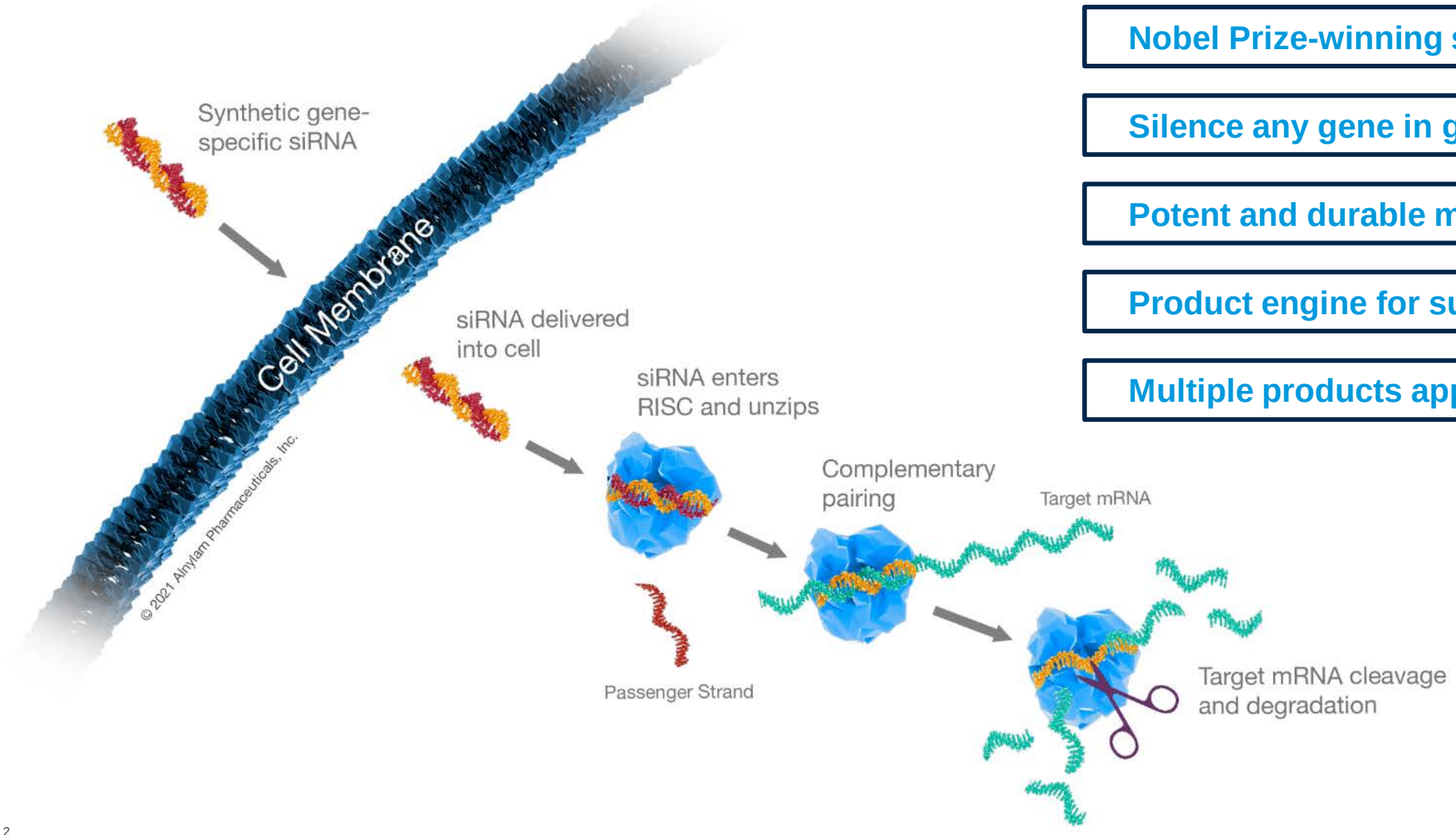
Alnylam PHARMACEUTICALS

RNAi Therapeutics: New Class of Medicines

Clinically and Commercially Established Approach



- **Nobel Prize-winning science**
- **Silence any gene in genome with siRNAs**
- **Potent and durable mechanism of action**
- **Product engine for sustainable innovation**
- **Multiple products approved & available globally**

Benson
Living with Primary Hyperoxaluria Type 1

Primary Hyperoxaluria Type 1

Lumasiran

Description

Rare autosomal recessive disorder of increased oxalate synthesis resulting in kidney stones and renal failure, with subsequent oxalate accumulation in extra-renal tissues

Onset generally

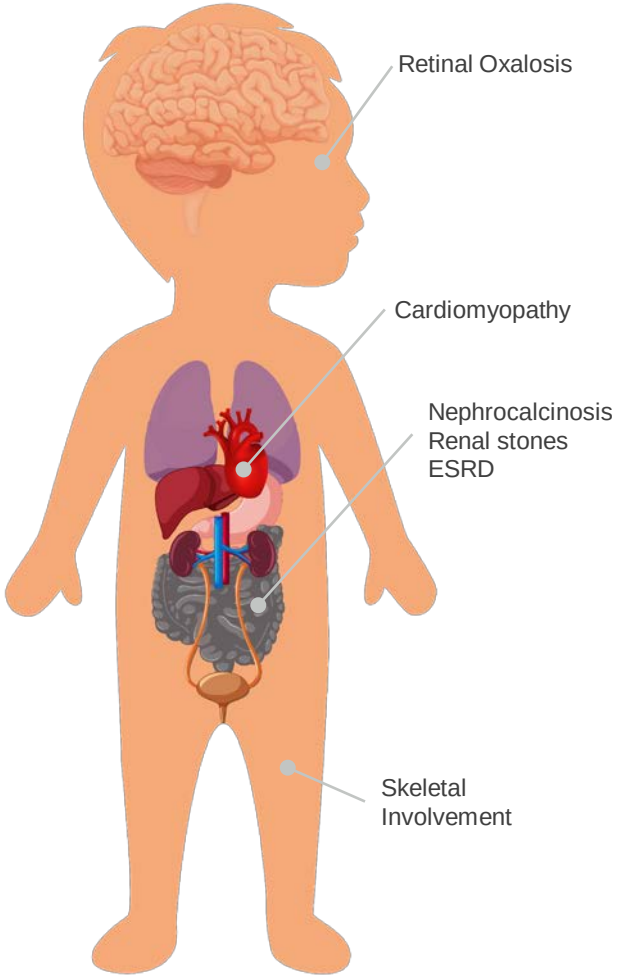
pediatric

very limited treatment options

Patient Population

~3,000

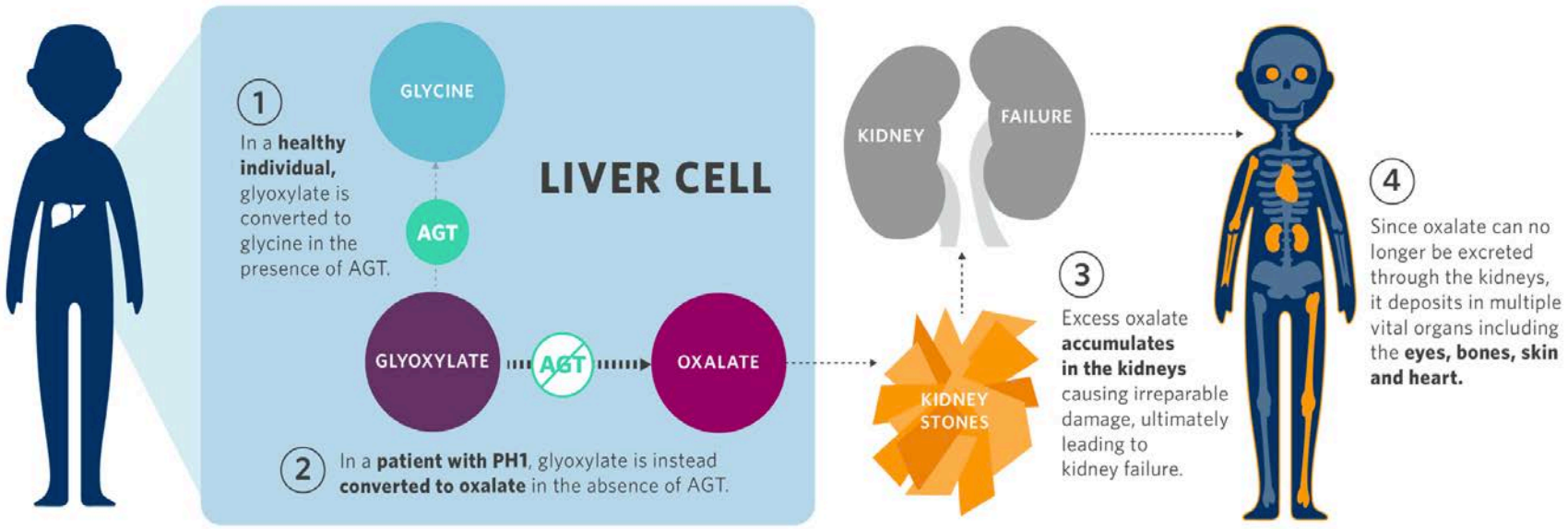
potentially symptomatic in U.S./EU[1]

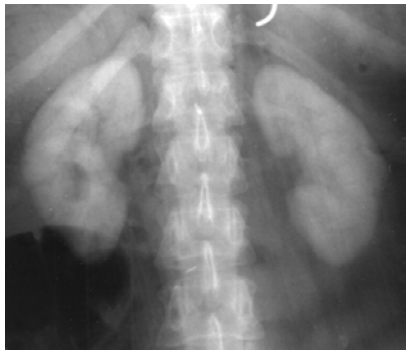


[1] Includes patients that are presymptomatic, subclinical, or symptomatic

PH1 Caused by a Hepatic Gene Mutation that Leads to Kidney Damage; Kidney Failure Then Results in Systemic Complications

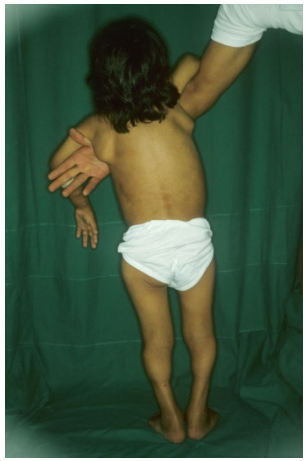
Mutation in alanine:glyoxylate aminotransferase (AGT)

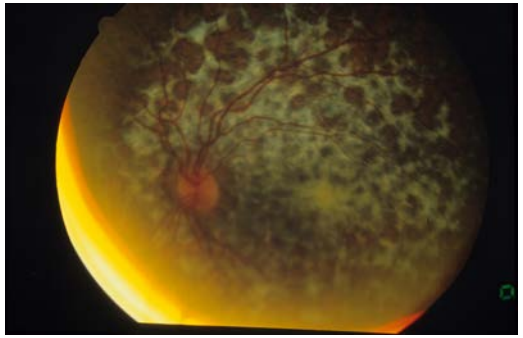




Bilateral nephrocalcinosis

Patient with bone deformities secondary to pathologic fractures



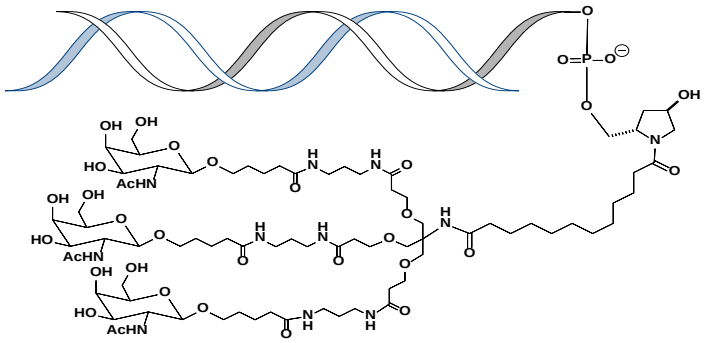


Retinal oxalosis

Lumasiran

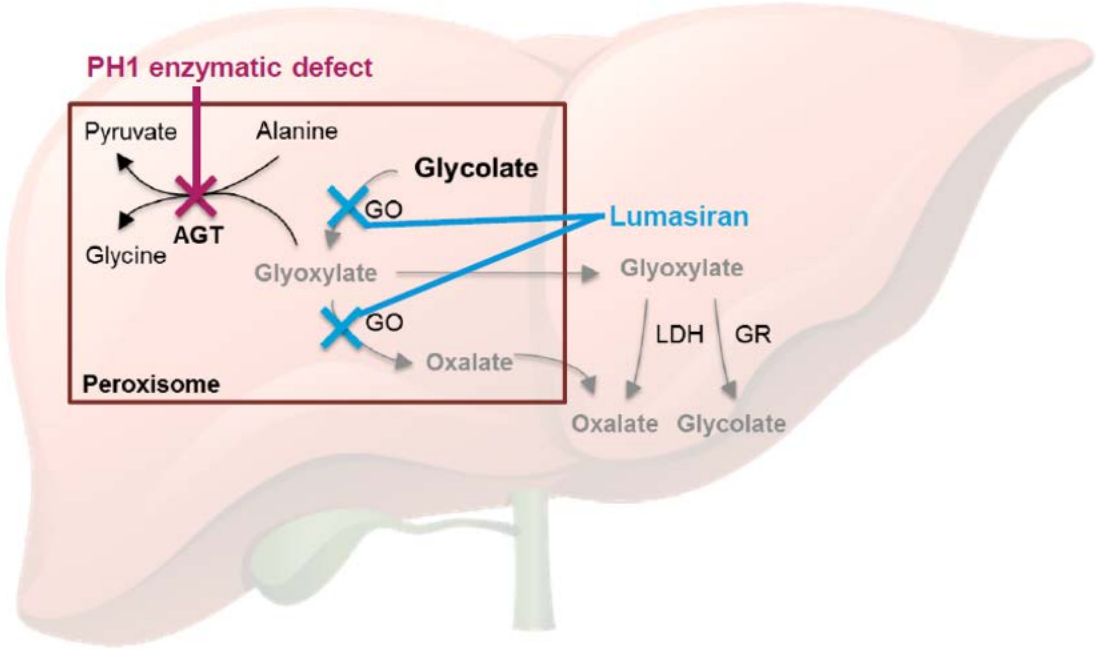
RNA interference Therapeutic for Primary Hyperoxaluria Type 1 (PH1)

- SC-administered GalNAc conjugated siRNA harnesses natural RNA interference (RNAi) mechanism
- Targets the mRNA for *HAO1* which encodes glycolate oxidase (GO) in the liver
- Decreased production of GO reduces hepatic oxalate production



Trivalent GalNAc Conjugated siRNA

Therapeutic Hypothesis:



HAO1, hydroxyacidoxidase 1
LiebowA, et al. *J Am Soc Nephrol*. 2017

Key Challenges in Developing Lumasiran for PH1

- Ultrarare disease
  - Small numbers of patients for clinical trials
  - Limited natural history data
  - No previously approved drugs → no regulatory precedent

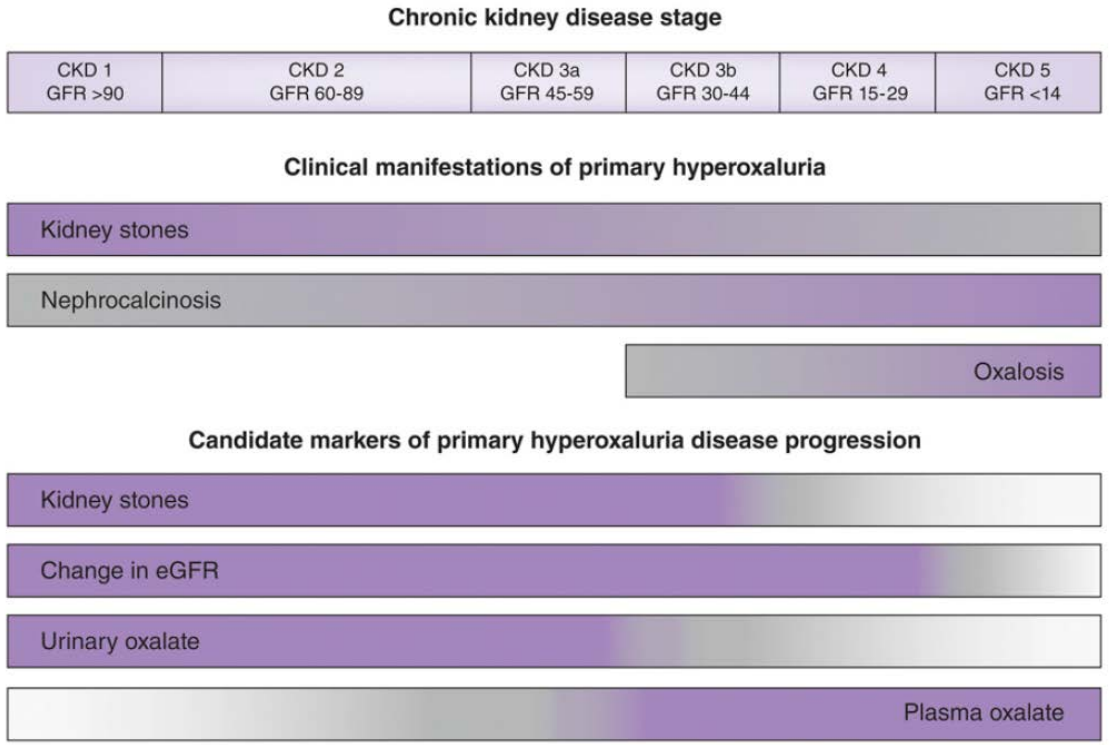
- Multiple patient segments:
  - All ages: Infants, children and adults
  - Full range of renal function: Completely intact to end-stage renal disease (including hemodialysis)

- Choice of endpoints:
  - Not feasible to power a study to clinical endpoints (eg, renal stones, renal function decline, manifestations of systemic oxalosis)
  - Measures of oxalate (urine, plasma) have high face validity and correlate with outcomes
    - Minimal clinically important difference (MCID) not defined
    - Available assays were diagnostic grade only

End Points for Clinical Trials in Primary Hyperoxaluria

Dawn S. Milliner,[1] Tracy L. McGregor,[2] Aliza Thompson,[3] Bastian Dehmel,[4] John Knight,[5] Ralf Rosskamp,[6] Melanie Blank,[3] Sixun Yang,[7] Sonia Fargue,[5] Gill Rumsby,[8] Jaap Groothoff,[9] Meaghan Allain,[10] Melissa West,[10] Kim Hollander,[11] W. Todd Lowther,[12] and John C. Lieske[1]

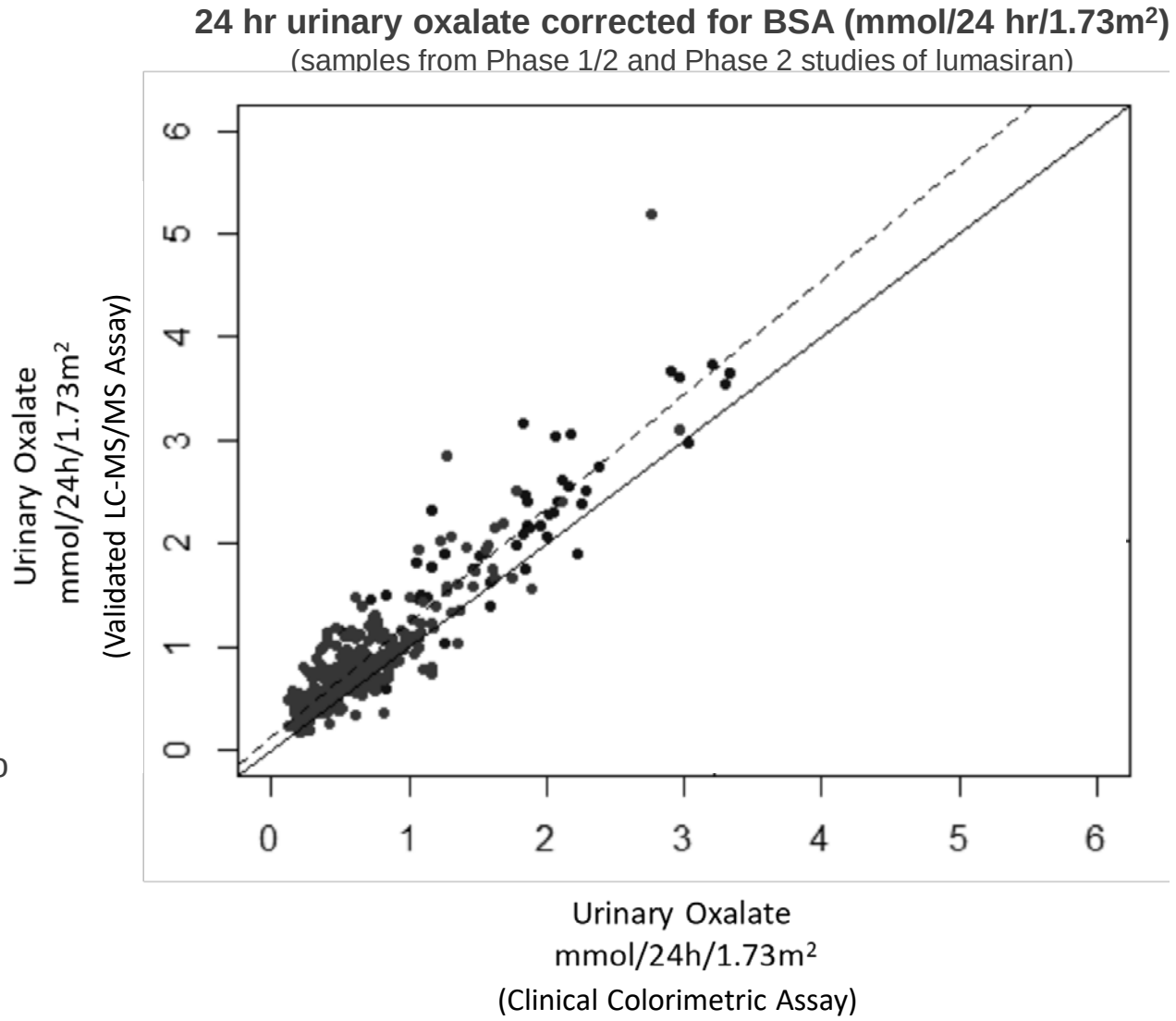
- The Kidney Health Initiative sponsored a collaborative effort of advocacy organizations, clinicians, scientists, pharmaceutical companies, and the FDA to evaluate potential surrogate endpoints for use in primary hyperoxaluria to establish efficacy and facilitate efficient approval.
- The workgroup concluded that urinary oxalate is reasonably likely to predict clinical benefit, due to its causal role in stone formation and kidney damage in CKD stages 1–3a, and plasma oxalate is likely associated with risk of systemic oxalosis in CKD 3b–5



Milliner D, et al. *Clin J Am Soc Nephrol.* 2020; 15(7): 1056-1065.

Urinary Oxalate Assays Used in Clinical Trials of Lumasiran

- Enzymatic assay used in the Phase 1/2 study
  - Used clinically for diagnosis and clinical management
  - Available at multiple clinical labs
- Validated LC-MS/MS assay used in all Phase 3 studies
  - Developed by Alnylam to meet FDA and EMA regulatory requirements
  - Assay range: 5.00–250 µg/mL (0.0555–2.78 mmol/L)
- Pearson correlation between the two methods is 0.925
- LC-MS/MS assay values are higher than those of enzymatic assay; however, Phase 2 OLE 24 hr urinary oxalate percent reduction is consistent between the two



BSA, body surface area; EMA, European Medicines Agency; FDA, US Food and Drug Administration; hr, hour; LC-MS, liquid chromatography-mass spectrometry; MS, mass spectrometry

Broad Clinical Development Plan to Address Spectrum of PH1 Patients

Clinical pharmacology study → **Efficacy and safety studies in patients with PH1**

Phase 1/2

STUDY 001

Healthy volunteers

Part A: single ascending dose, n=32

Primary endpoint
- Safety

COMPLETED

PH1 patients

Part B: multiple ascending doses, n=20
- 6–64 years old
- eGFR >45 mL/min/1.73 m^2
- Up to 3 doses

Primary endpoint
- Safety

COMPLETED

STUDY 002
OLE
n=20
Up to 54 months' dosing

Phase 3

ILLUMINATE-A

PH1 patients

Double-blind, placebo-controlled, n=39
- ≥6 years old
- eGFR ≥30 mL/min/1.73 m^2
- 6-month dosing

Primary endpoint
- Percent change in 24 hr urinary oxalate excretion from baseline through month 6

COMPLETED

EXTENSION PERIOD
Up to 54 months' dosing

ILLUMINATE-B

PH1 patients

Single-arm, open-label n=18
- <6 years old
- eGFR[a] >45 mL/min/1.73 m^2
- 6-month dosing

Primary endpoint
- Percent change from baseline in urinary oxalate excretion through month 6

COMPLETED

EXTENSION PERIOD
Up to 54 months' dosing

ILLUMINATE-C

PH1 patients

Single-arm, open-label n=21
- All ages
- eGFR[b] ≤45 mL/min/1.73 m^2
- 6-month dosing

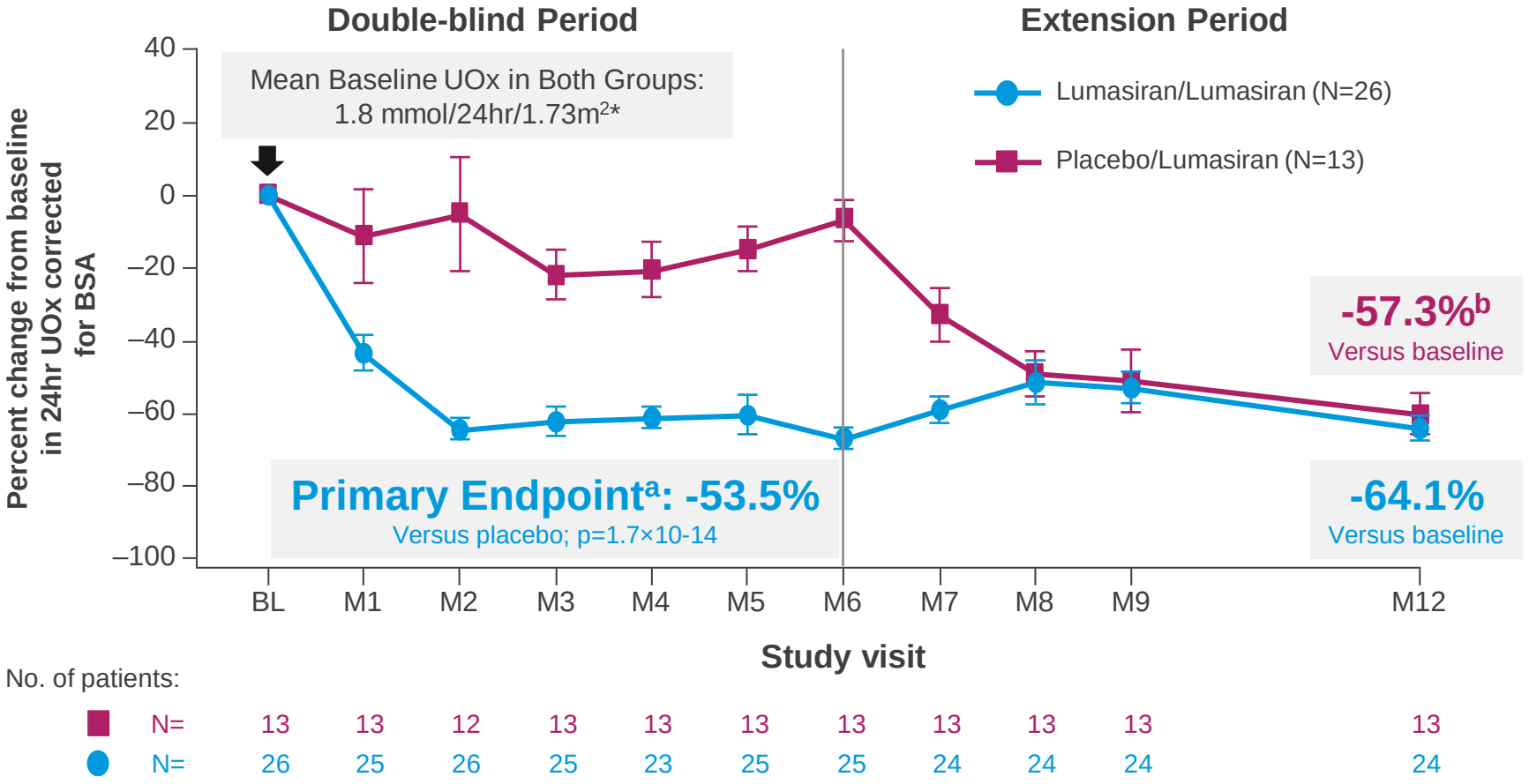
Primary endpoint
- Percent change in plasma oxalate from baseline to month 6

COMPLETED

EXTENSION PERIOD
Up to 54 months' dosing

[a] Normal serum creatinine if <12 months old; [b] Elevated serum creatinine if <12 months old
eGFR, estimated glomerular filtration rate; hr, hour; min, minute; OLE, open-label extension; PH1, primary hyperoxaluria type 1

ILLUMINATE•A: Percent Change in 24hr Urinary Oxalate



*ULN=0.514 mmol/24hr/1.73m² for 24-hour UOx corrected for BSA; eligibility criteria required UOx ≥0.7 mmol/24hr/1.73m²

[a]LS mean difference from baseline to Month 6 (average of Month 3 through Month 6). [b]Baseline is the median of all valid 24-hr urine assessments at Month 6 (or, if the patient does not have two valid assessments at Month 6, then the baseline is calculated using the latest three valid 24-hour urine collections)

Data in graph are mean ± SEM of observed values

BSA, body surface area; LS, least-squares; SEM, standard error of mean; UOx, urinary oxalate

ILLUMINATE•A: Lumasiran Safety Profile

- Overall mean exposure: 9.9 months (range 2.8–15.1 months) with 233 doses given
  - 35 patients treated for ≥6 months and 10 patients for ≥12 months
- Majority of AEs were mild in severity
- Most common related AEs (≥10%) were injection-site reactions, which were mild and transient
  - Erythema, pain, pruritus, or swelling at the injection site most common symptoms
- 1 patient with serious AE of urosepsis (severe), considered not related to study drug
- No treatment interruptions or discontinuations related to lumasiran; no deaths
- No clinically relevant changes in laboratory measures (including LFTs), vital signs, and electrocardiograms were observed

For additional information, see full Prescribing Information at www.OXLUMO.com

Event, n (%)	Placebo/ Lumasiran (N=13)	Lumasiran/ Lumasiran (N=26)	All Lumasiran (N=39)
AEs	9 (69)	24 (92)	33 (85)
Serious AE[a]	0	1 (4)	1 (3)
Severe AE[a]	0	1 (4)	1 (3)
AE leading to discontinuation of study treatment[b]	0	1 (4)	1 (3)
AEs occurring in ≥10% of patients			
Injection-site reactions[c]	5 (39)	11 (42)	16 (41)
Abdominal pain	1 (8)	6 (23)	7 (18)
Headache	0	4 (15)	4 (10)
Rhinitis	2 (15)	2 (8)	4 (10)
Upper respiratory infection	1 (8)	3 (12)	4 (10)
Death	0	0	0

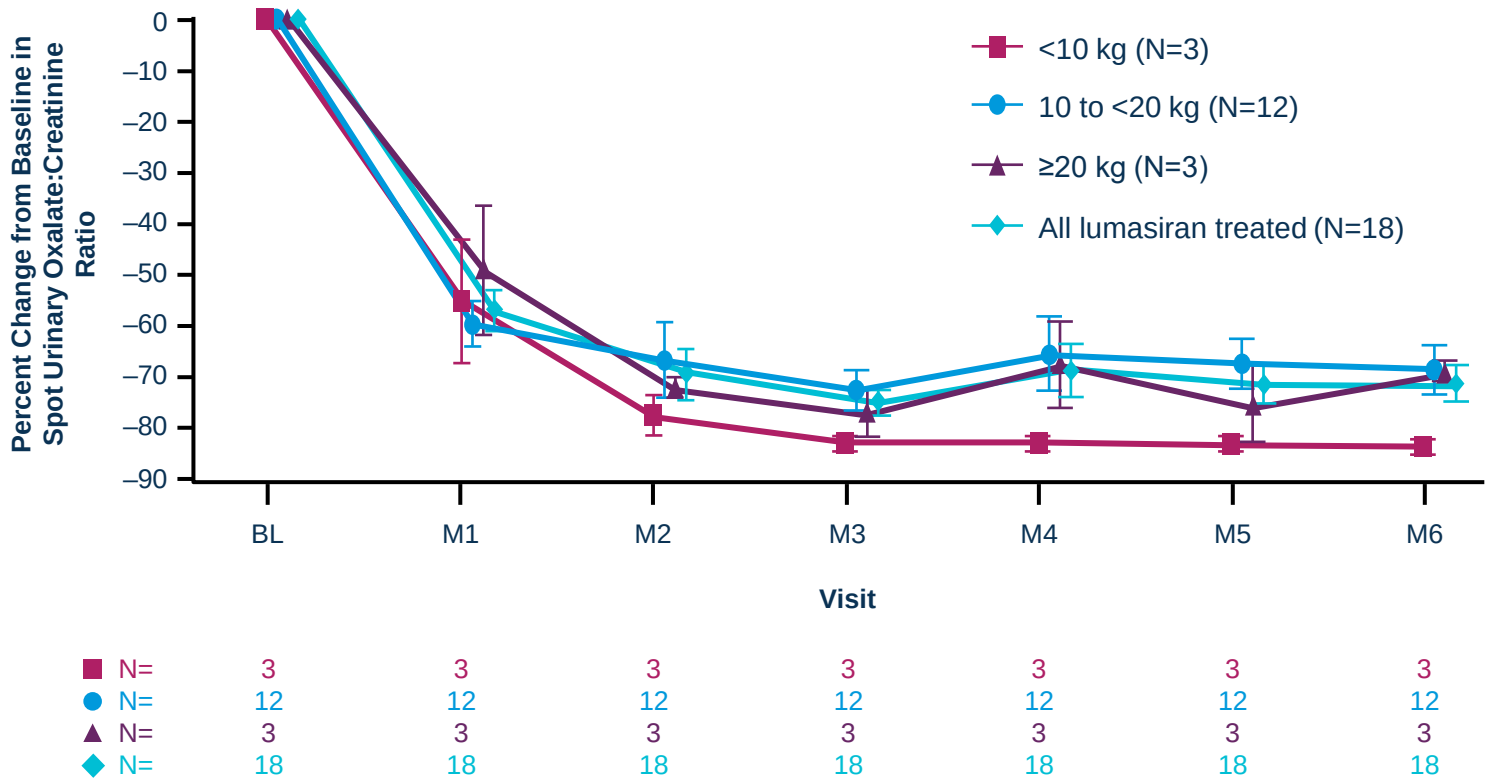
Safety data from first dose of lumasiran to data cut-off date: 1 May 2020.

[a]Urosepsis, considered not related to study drug by the Investigator. [b]Fatigue and disturbance in attention, considered not related to lumasiran by the Investigator. [c]Includes adverse events of injection-site reaction, injection-site pain, injection-site erythema, and injection-site discomfort

AE, adverse event; LFT, liver function test; PH1, primary hyperoxaluria type 1

ILLUMINATE•B: Single-Arm Phase 3 Study of Lumasiran in Patients < 6 yo with Preserved Renal Function

Primary Endpoint: Percent Change in Urinary Oxalate Excretion from Baseline to Month 6



-72.0%[a]
Versus baseline

Rapid and Sustained Reduction in Spot Urinary Oxalate:Creatinine Ratio Across All Weight Groups

[a]LS mean reduction from baseline to Month 6 (average of Month 3 through Month 6)
Data in graph are presented as mean ± SEM of observed values
BL, baseline; LS, least-squares; M, month; SEM, standard error of the mean; ULN, upper limit of normal

ILLUMINATE-B: Lumasiran Safety Profile During 6-Month Treatment Period

- No deaths, discontinuations or withdrawals, or severe AEs
- One serious AE occurred which was considered not related to lumasiran[a]
- Most common drug-related AE was injection-site reactions in 3 (17%) patients; all were mild and transient
- No clinically relevant changes in laboratory measures, vital signs, or electrocardiograms related to lumasiran were observed
- No hepatic events were reported

Event, n (%)	<10 kg (N=3)	10 to <20 kg (N=12)	≥20 kg (N=3)	All Treated (N=18)
At least 1 AE	3 (100)	12 (100)	3 (100)	18 (100)
At least 1 drug-related AE Injection-site reaction Headache	0 0 0	2 (17) 2 (17) 0	2 (67) 1 (33) 1 (33)	4 (22) 3 (17) 1 (6)
At least 1 serious AE	0	0	1 (33)[a]	1 (6)[a]
At least 1 severe AE	0	0	0	0
Discontinuations/ withdrawal	0	0	0	0
Death	0	0	0	0

Safety data from first dose of lumasiran to data cut-off date: 30 June 2020.

For additional information, see full Prescribing Information at www.OXLUMO.com

[a]Viral infection, considered not related to the study drug by the Investigator
AE, adverse event; SAE, serious adverse event

Active Involvement with the Advocacy Community

NATIONAL KIDNEY FOUNDATION®

APHES
Asociación de Pacientes de Hiperoxaluria España

METABOLIC SUPPORT UK
Your rare condition. Our common fight.

PH
PRIMARY HYPEROXALURIA

American Kidney Fund®
FIGHTING ON ALL FRONTS

FDA NEWS RELEASE

FDA Approves First Drug to Treat Rare Metabolic Disorder

Approval is for primary hyperoxaluria type 1, which causes recurrent kidney stones and loss of kidney function

For Immediate Release:

November 23, 2020

Today, the U.S. Food and Drug Administration approved Oxlumo (lumasiran) as the first treatment for primary hyperoxaluria type 1 (PH1), a rare genetic disorder. This approval is a cumulation of the work of experts and community members coordinated by the Oxalosis & Hyperoxaluria Foundation and the Kidney Health Initiative.

"The approval of Oxlumo represents a great triumph of community involvement to address a rare disease. It is a result of input from patients, treating physicians, experts and sponsors at a patient-focused drug development meeting and through other collaborative efforts," said Norman Stockbridge, M.D., Ph.D., director of the Division of Cardiology and Nephrology in the FDA's Center for Drug Evaluation and Research.

ILLUMINATE•C: Single-Arm Phase 3 Study of Lumasiran in Advanced PH1

Topline Results

- **Substantial reductions in plasma oxalate relative to baseline**
  - Both in dialysis-independent and -dependent patients
- **Encouraging safety and tolerability profile**
  - No deaths or drug related SAEs
  - Most common AEs were ISRs in 5 patients (23.8%), all of which were mild
  - Two discontinuations due to AEs, both occurring during extension period and neither related to study drug
- **Supplemental regulatory filings expected to be submitted to FDA and EMA in late 2021**

Summary

- Primary Hyperoxaluria Type 1 (PH1) is a rare, autosomal recessive disorder caused by mutations in the hepatically-expressed gene, AGT, that results in excess hepatic oxalate production leading to renal failure and ultimately, systemic oxalosis.

- Lumasiran is a hepatically-directed, RNAi therapeutic designed to reduce expression of glycolate oxidase, thereby lowering hepatic oxalate production

- Successful development of lumasiran for PH1 depended heavily on extensive input and contributions from key stakeholders in the patient advocacy, physician, and regulatory communities which lead to a rapid and full approval based on novel biomarker-based endpoints