Lumasiran, in Development for the Treatment of Primary Hyperoxaluria Type 1

October 10, 2019

RNAi ROUNDTABLE 2019

Alnylam® PHARMACEUTICALS

Agenda

Welcome
- Joshua Brodsky – Director, Investor Relations & Corporate Communications

Introduction
- Pritesh Gandhi, PharmD. – Vice President, General Manager, Lumasiran

Primary Hyperoxaluria Type 1 & Physician Perspective
- Elaine M. Worcester, M.D. – Nephrologist & Professor of Medicine, University of Chicago Medicine

Patient & Caregiver Perspective
- Andrew – Patient Diagnosed with Primary Hyperoxaluria Type 1
- Nicole – Andrew's Wife and Caregiver

Early Stage Clinical Data & ILLUMINATE Studies
- Kenji Fujita, M.D. – Vice President, Clinical Development

Lumasiran Program Opportunity in PH1 & Disease Education/Diagnosis Initiatives
- Pritesh Gandhi, PharmD. – Vice President, General Manager, Lumasiran

Q&A Session

Reminders

Event will run for approximately 60-75 minutes

Q&A session at end of presentation

- Questions may be submitted at any time via the ‘Ask a Question’ field on the webcast interface.

Replay, slides and transcript available at www.alnylam.com/capella

Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates, including lumasiran; pre-clinical and clinical results for our product candidates, including lumasiran; actions or advice of regulatory agencies, including with respect to lumasiran; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; the timing of regulatory submissions for our product candidates, including lumasiran, and our ability to obtain and maintain regulatory approval, pricing and reimbursement for such products, including lumasiran; our progress in establishing a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally, including lumasiran if approved by regulatory agencies; competition from others using similar technology and developing products for similar uses; as well as those risks more fully discussed in our most recent report on Form 10-Q under the caption "Risk Factors." If one or more of these factors or risks materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. The safety and efficacy of lumasiran are being evaluated in the ILLUMINATE Phase 3 program and have not yet been reviewed by the FDA, EMA or any other regulatory agency. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

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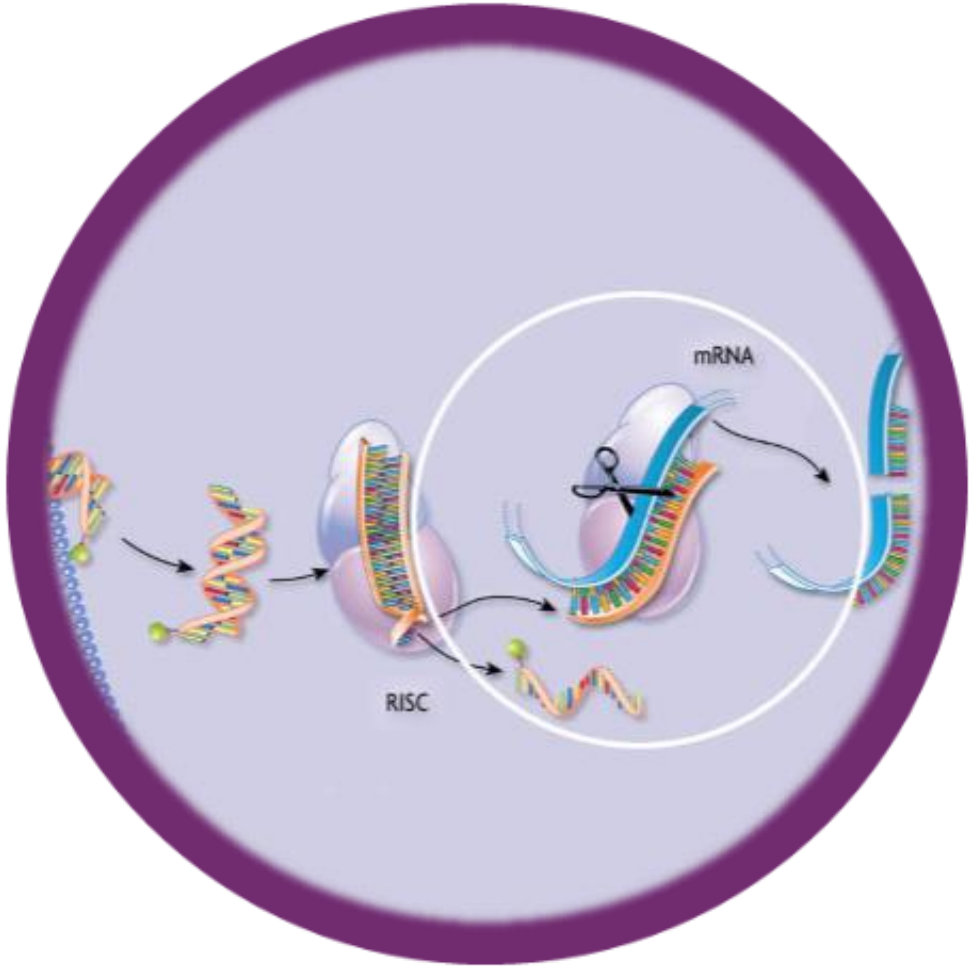
RNAi Therapeutics: New Class of Innovative Medicines

Clinically Proven Approach with Transformational Potential

- Nobel Prize-winning science
- Silence any gene in genome
- Potent and durable mechanism of action
- Product engine for sustainable pipeline
- Now commercial



Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

Genetic Medicines · Cardio-Metabolic Diseases · Hepatic Infectious Diseases · CNS/Ocular Diseases

		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	EARLY STAGE *(IND or CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 4)*	REGISTRATION/ COMMERCIAL[3]	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis*[2]	✓	●			●	Global
Givosiran	*Acute Hepatic Porphyria*	✓	●			●	Global
Patisiran	*ATTR Amyloidosis Label Expansion*	✓			●		Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*	✓			●		15-30% royalties
Inclisiran	*Hypercholesterolemia*	✓			●		Milestones & up to 20% royalties
Lumasiran	*Primary Hyperoxaluria Type 1*	✓	●		●		Global
Vutrisiran	*ATTR Amyloidosis*	✓			●		Global
Cemdisiran	*Complement-Mediated Diseases*	✓		●			50-50
Cemdisiran/Pozelimab Combo[4]	*Complement-Mediated Diseases*			●			Milestone/Royalty
ALN-AAT02	*Alpha-1 Liver Disease*			●			Global
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*			●			50-50 option rights post-Phase 2
ALN-AGT	*Hypertension*			●			Global

[1] POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies

[2] Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU and Switzerland for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy

[3] Includes marketing application submissions

[4] Cemdisiran is currently in Phase 2 development and pozelimab is currently in Phase 1 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics

As of October 2019

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Primary Hyperoxaluria Type 1

Rare Genetic Disorder of Increased Endogenous Oxalate Synthesis

Primary Hyperoxaluria Type 1 (PH1):

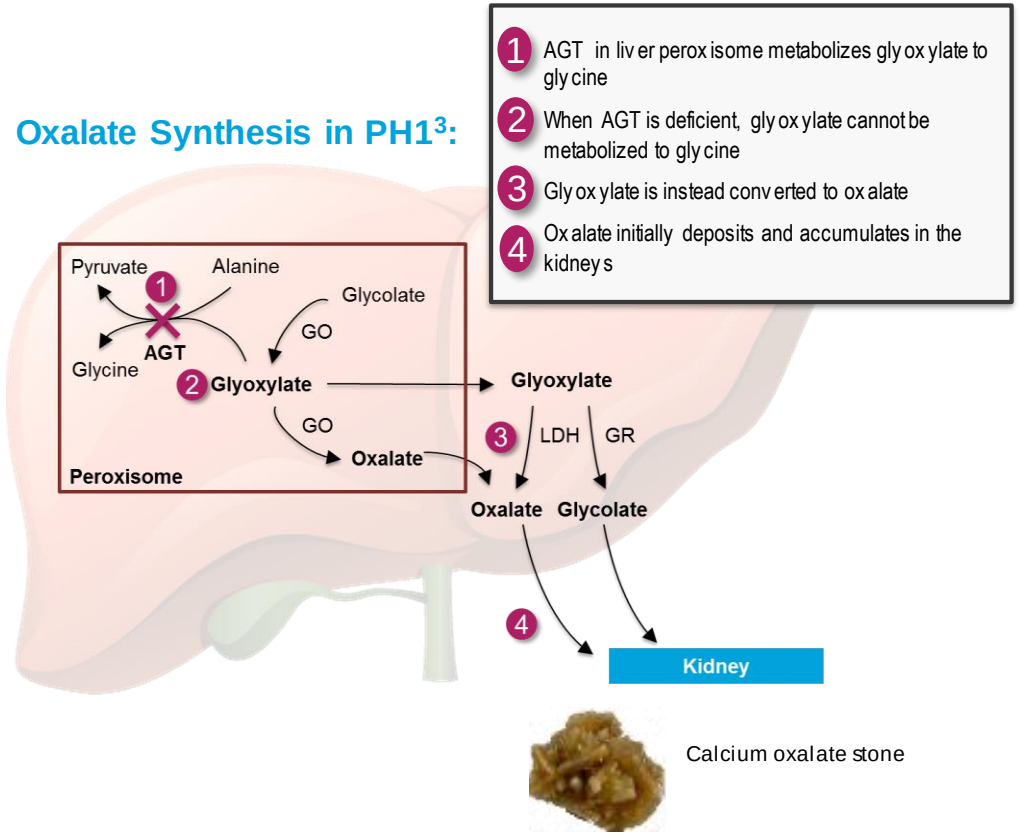
- Due to defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- Phenotype varies significantly in patients and may present at any age, typically in childhood
- Prevalence of PH1: 1-3/1,000,000 in Europe[1] and ~ 32/1,000,000 in Middle East[2]

Pathophysiology[1]:

- Overproduction of oxalate results in insoluble calcium oxalate crystals leading to urolithiasis, nephrocalcinosis, and kidney failure
- Disease course ultimately leads to multi-organ damage from systemic oxalosis

No therapies are approved for treatment of PH1

Oxalate Synthesis in PH1[3]:



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.

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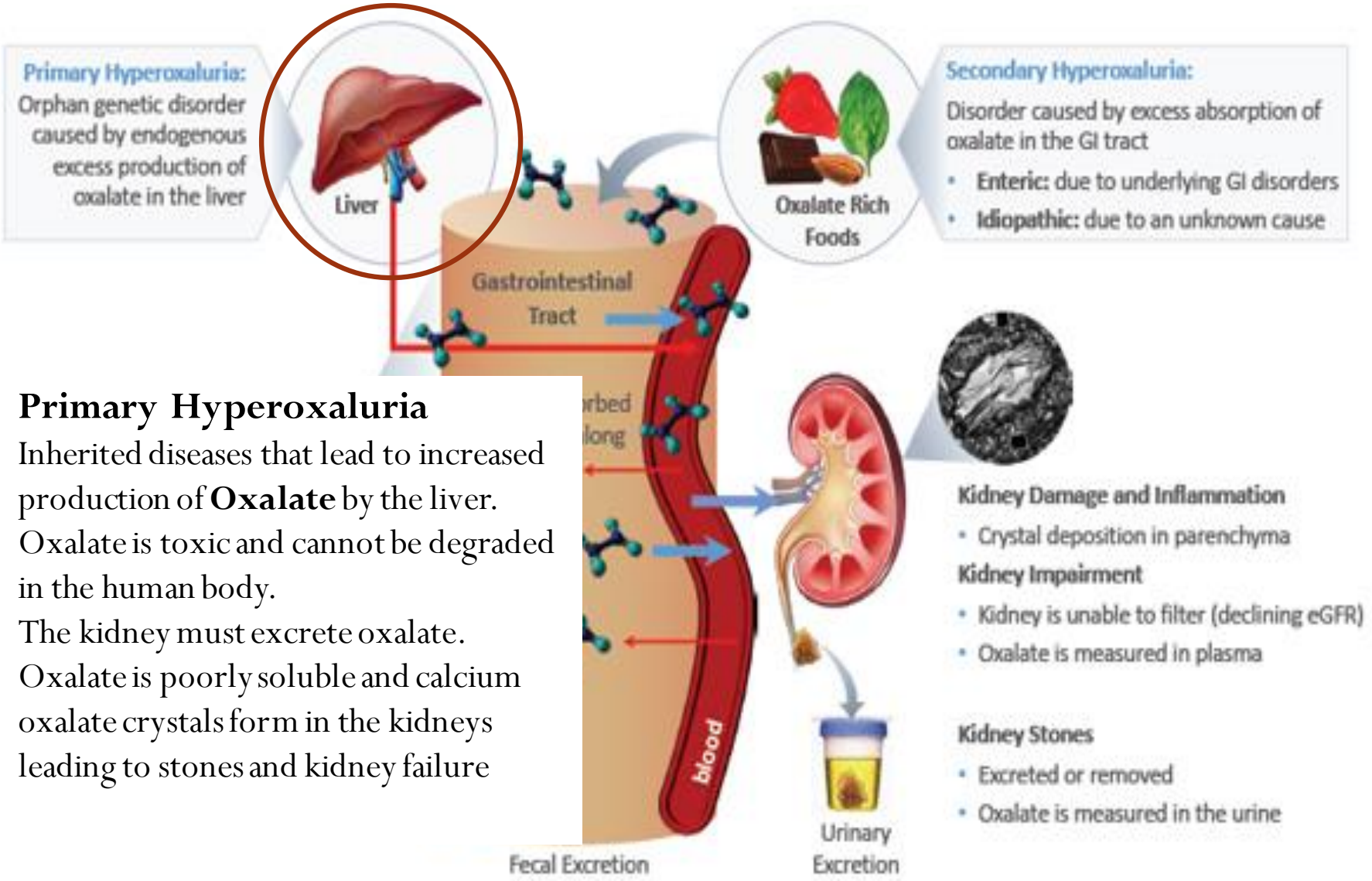
Primary Hyperoxaluria

Elaine Worcester, MD
University of Chicago,
Chicago, Illinois, USA



Primary Hyperoxaluria

Inherited diseases that lead to increased production of **Oxalate** by the liver.

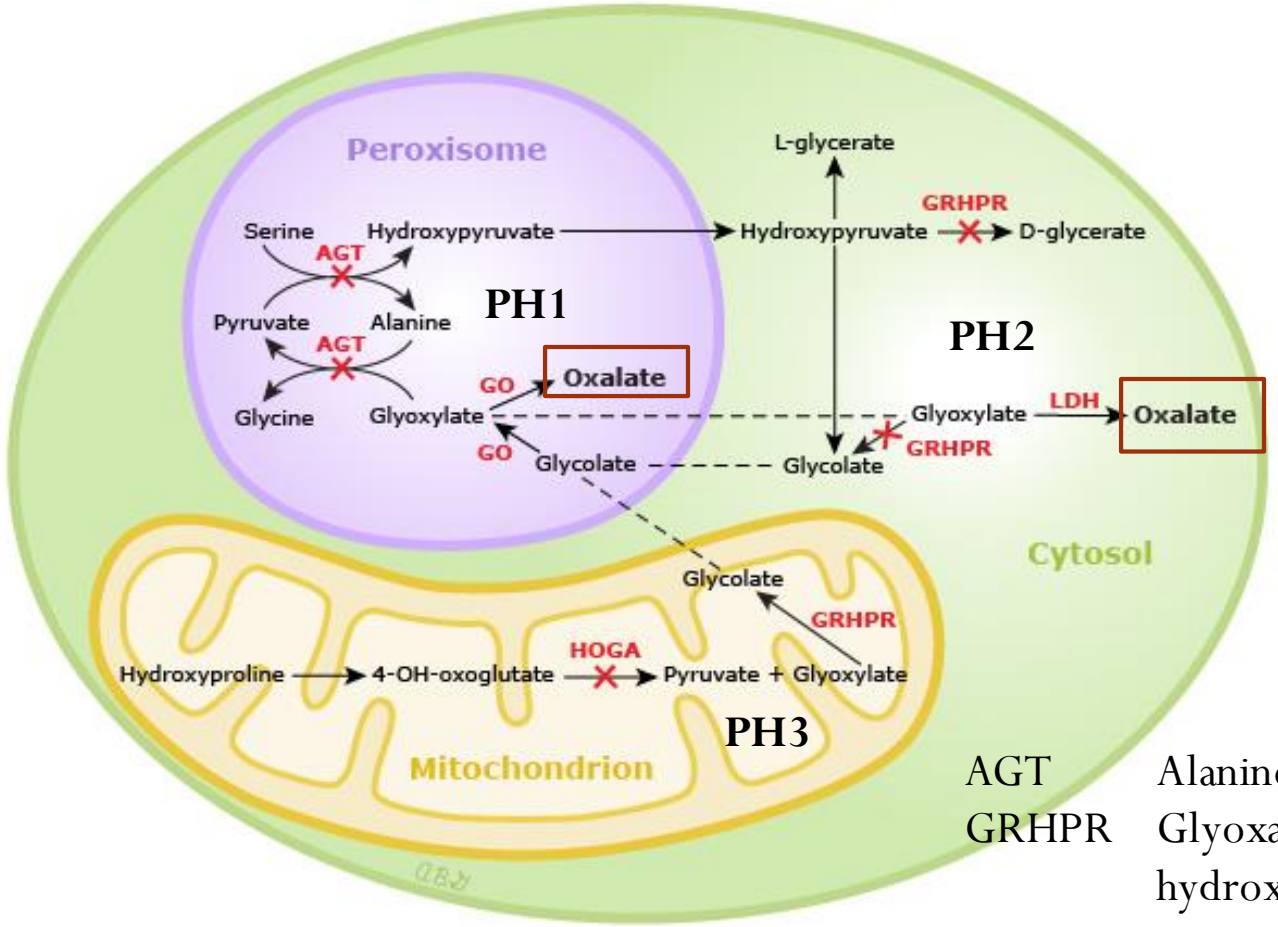
Oxalate is toxic and cannot be degraded in the human body.

The kidney must excrete oxalate.

Oxalate is poorly soluble and calcium oxalate crystals form in the kidneys leading to stones and kidney failure

Hyperoxaluria is an under-recognised metabolic disorder characterized by markedly elevated urinary oxalate levels. Illustration adapted from Coe, Fred. "Control of Urine Oxalate Excretion." Kidneystones.uchicago.edu. University of Chicago, kidneystones.uchicago.edu/control-of-urine-oxalate-excretion. March 2017.

Genetic defects in glyoxylate metabolism resulting in the three types of primary hyperoxaluria (PH)



PH1 (80% of cases)
Absence or decreased activity of AGT

PH2 (10% of cases)
Absence or decreased activity of GRHPR

PH3 (5% of cases)
Absence of HOGA

AGT	Alanine:glyoxylate aminotransferase
GRHPR	Glyoxalate reductase/ hydroxypyruvate reductase
HOGA	4-hydroxy-2-oxoglutarate aldolase

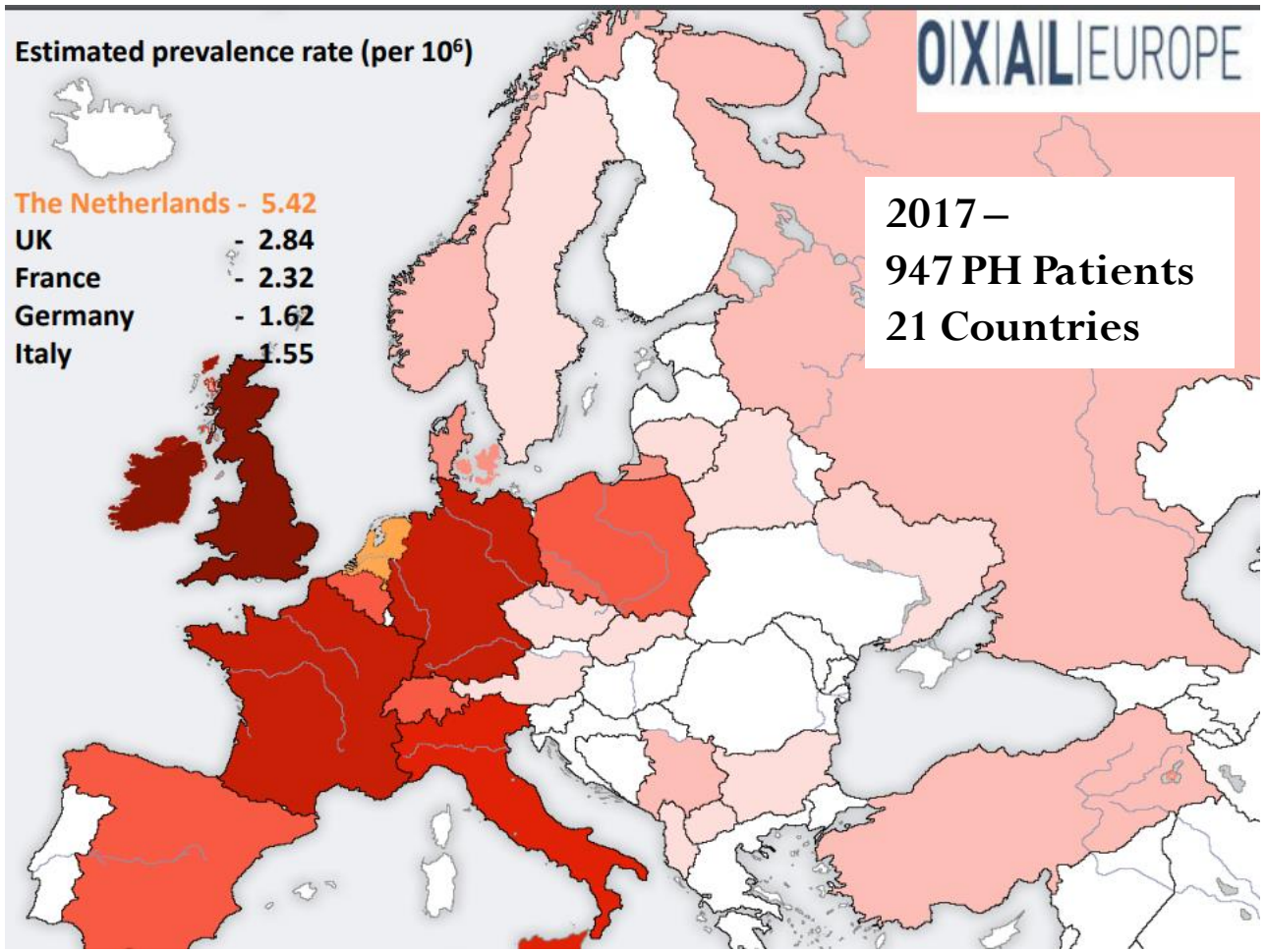
Prevalence data from Rare Kidney Stone Consortium

Prevalence of PH1

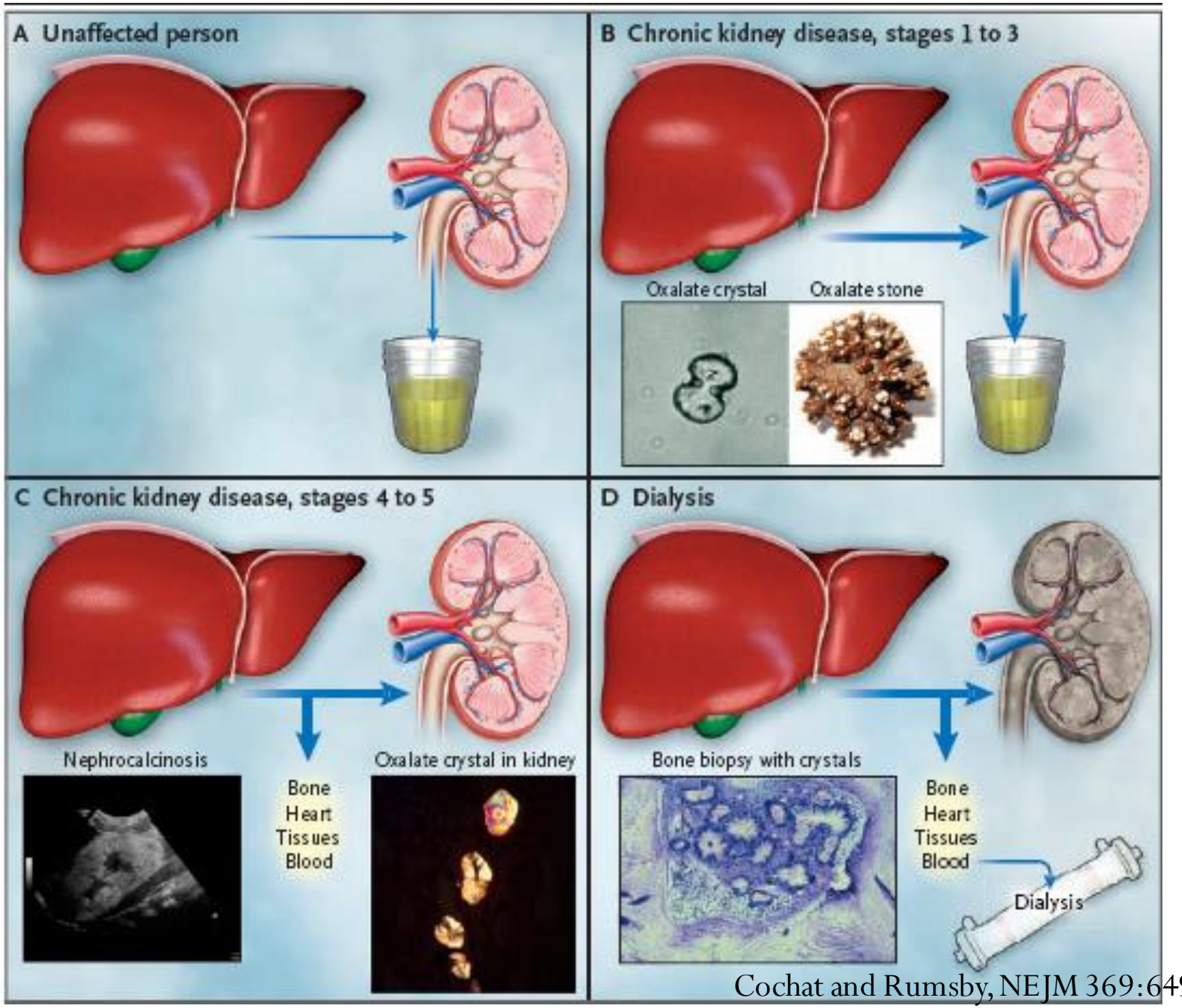
PH1 prevalence estimated at 1-3 cases/million people in Europe.

Prevalence is increased in countries with high rates of consanguineous marriages, such as the Middle East, Pakistan and North Africa.

PH1 causes about 1-2% of pediatric ESRD in Europe, but 17% in Tunisia.



OxalEurope data, thanks to SF Garrelfs

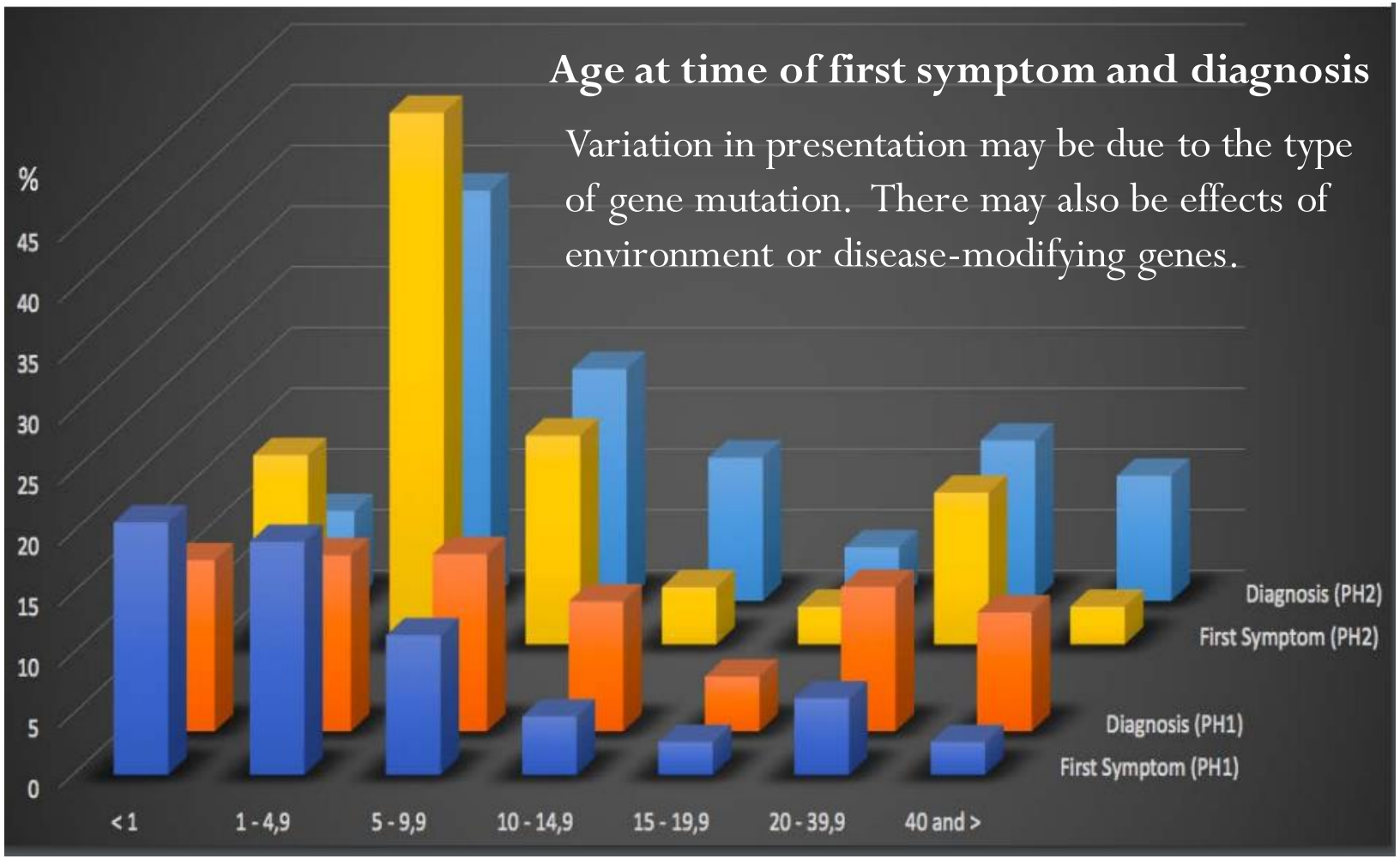


Stages of disease in PH1

Cochat and Rumsby, NEJM 369:649. 2013

Patterns of presentation of PH:

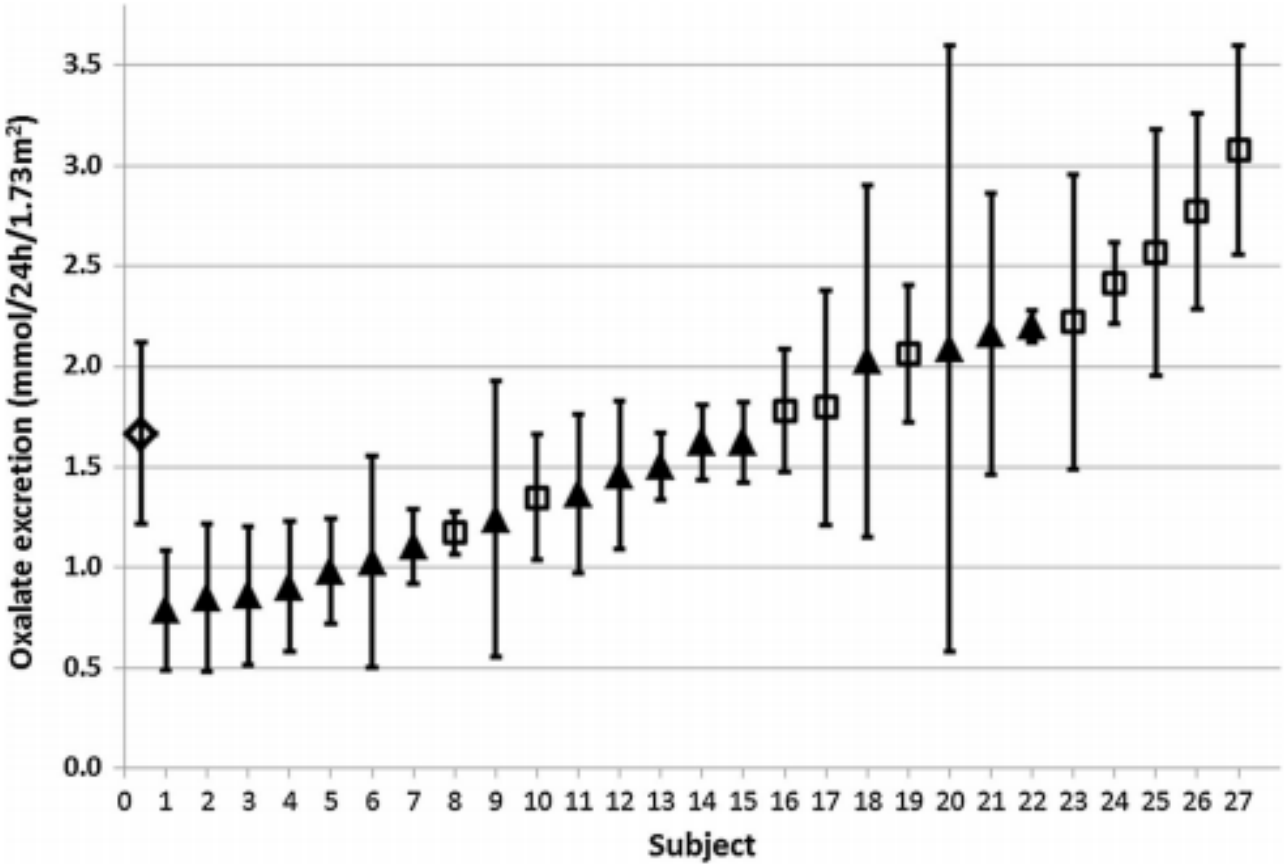
1. Infantile oxalosis (26%) with nephrocalcinosis, failure to thrive, UTI. ESRD mean age 3 yr.
2. Childhood (30%) with frequent kidney stones, chronic kidney disease
3. Stone formation in adulthood (30%)
4. Recurrence after transplant for ESRD of unknown cause (10%)
5. Diagnosis after family screening (13%)



Range of oxalate excretion in PH1

Fig. 1 Range of oxalate excretion from the four 24 h urines collected by each subject. Points represent means and error bars ±2SDs. The *open diamond* is the average of all 27 subjects, *closed triangles* are subjects taking pyridoxine, and *open squares* are subjects not taking pyridoxine

▲ Taking pyridoxine



One subject each of PH2 and PH3 included

Mobley et al Urolithiasis 44: 333, 2016

Urine oxalate:creatinine ratios from patients ≥ 5 years old

(Normal < 50 at age 5, < 25 by age 20)

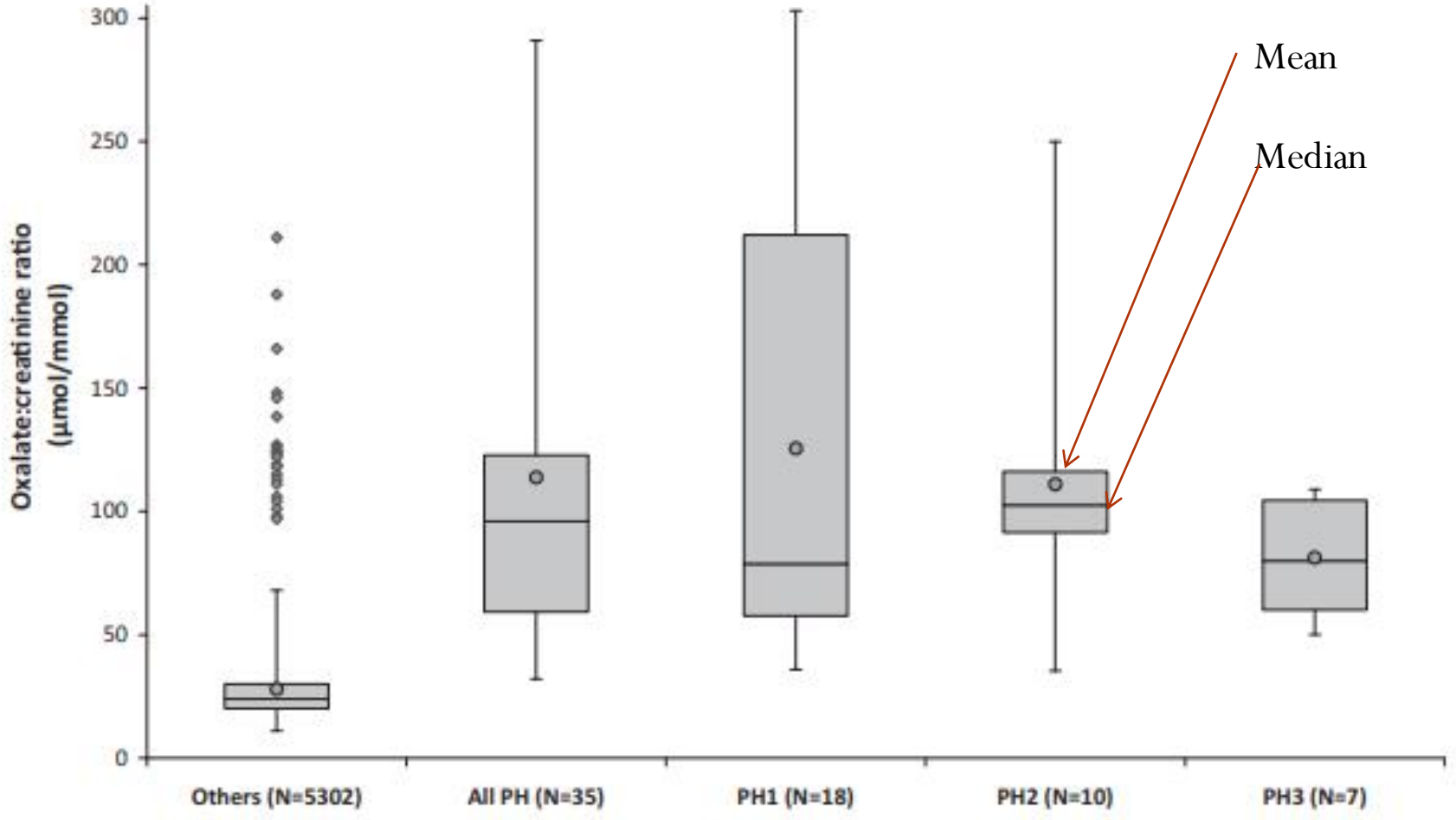
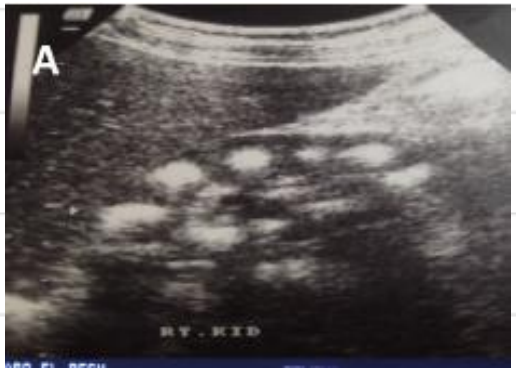


Figure 3. Box and whisker plot of oxalate:creatinine ratios from patients aged five years or over, stratified according to diagnosis (PH1, PH2, PH3, all PH and 'Others'). The circle represents the mean, the horizontal line the median, the box the interquartile range, the whiskers the 2.5th and 97.5th percentiles and the diamonds the 24 patients from the 'others' group with grossly elevated results.

Symptoms at time of diagnosis

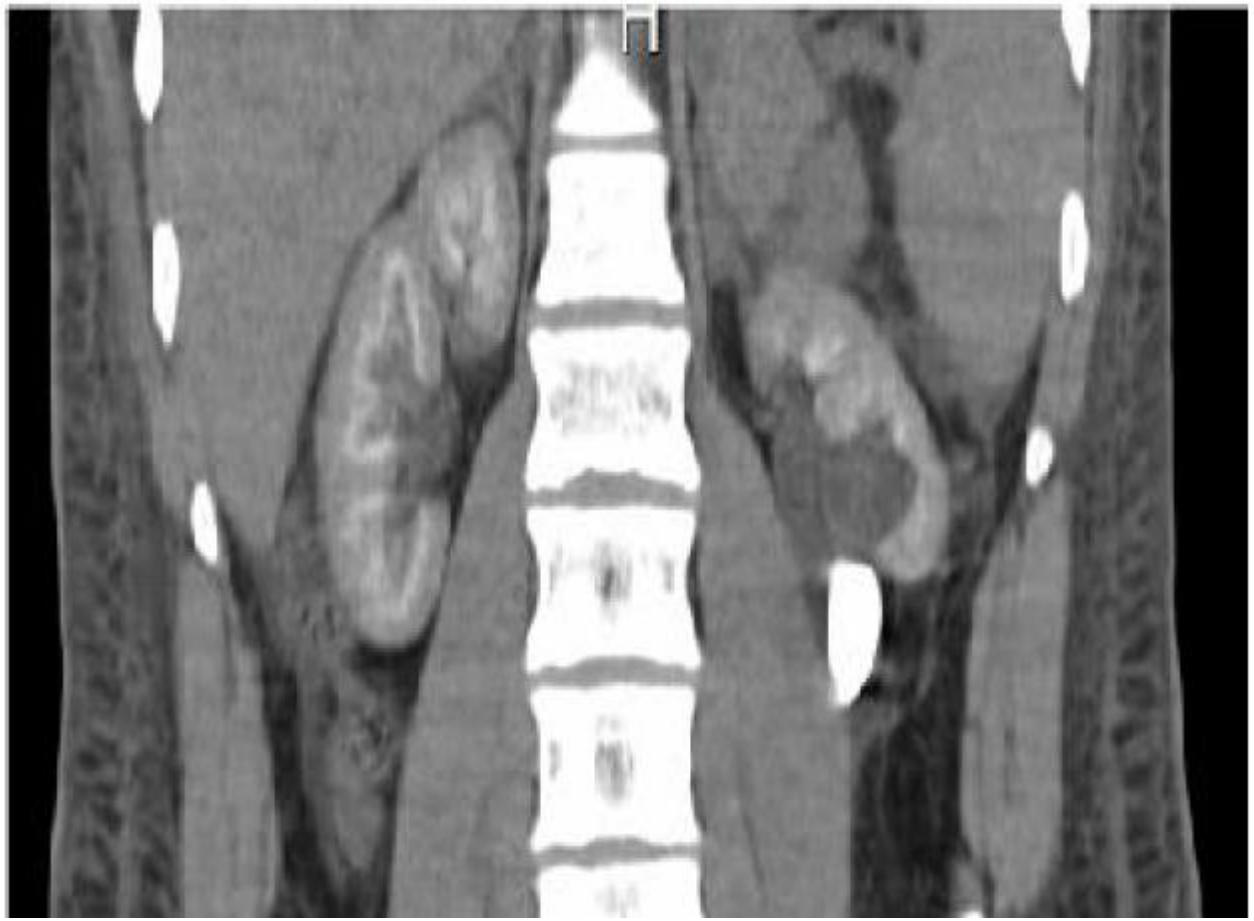


Median age at symptom onset 4-5 years
Early diagnosis facilitates treatment to decrease stones and nephrocalcinosis and delay ESRD.

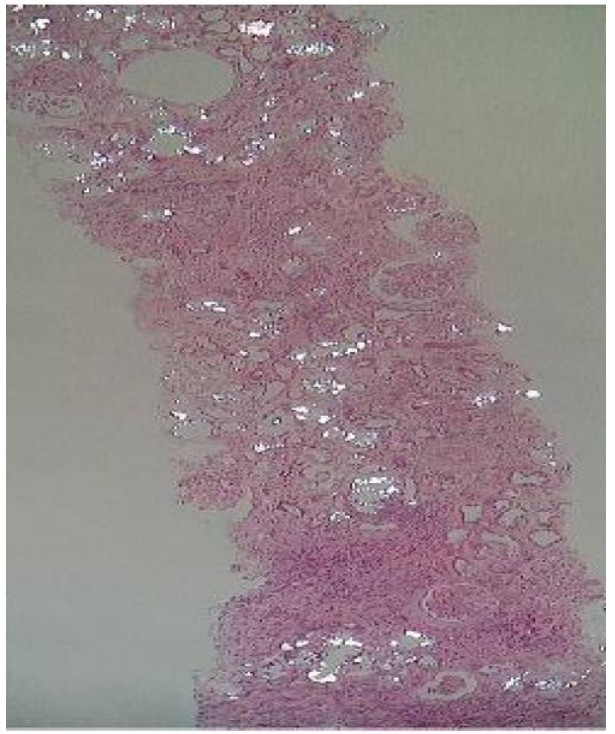
ESRD at diagnosis
< 18 yr – 34%
> 18 yr – 74%

25 yr old man presented with severe acute kidney failure after strenuous exercise

Normal kidney function 3 months earlier, no clinical history of stones



Kidney biopsy



El-Reshaid et al. Saudi J Kid Dis Tranpl 2016

ESRD in Primary Hyperoxaluria

N= 409 patients (73% with PH1)

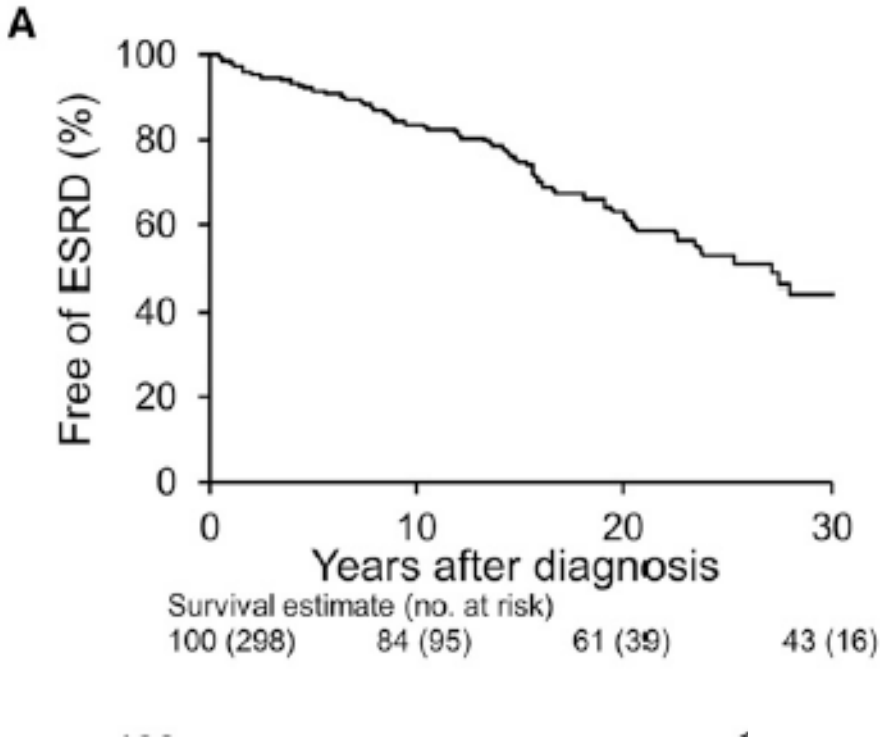
Renal survival in 297 patients without ESRD at diagnosis

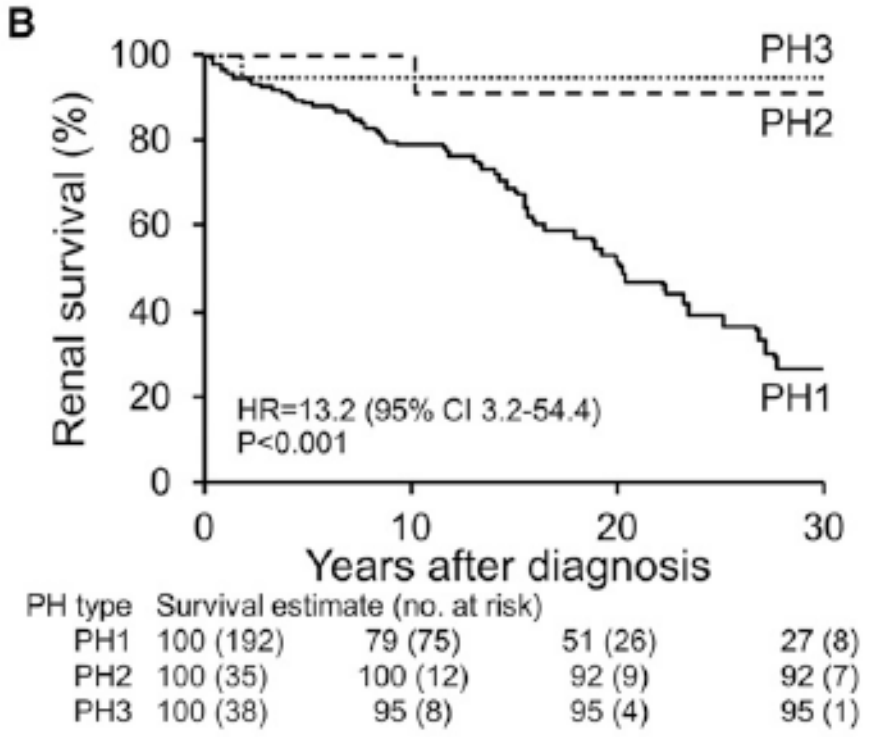
112 patients presented with ESRD:

PH1 35%

PH2 10%

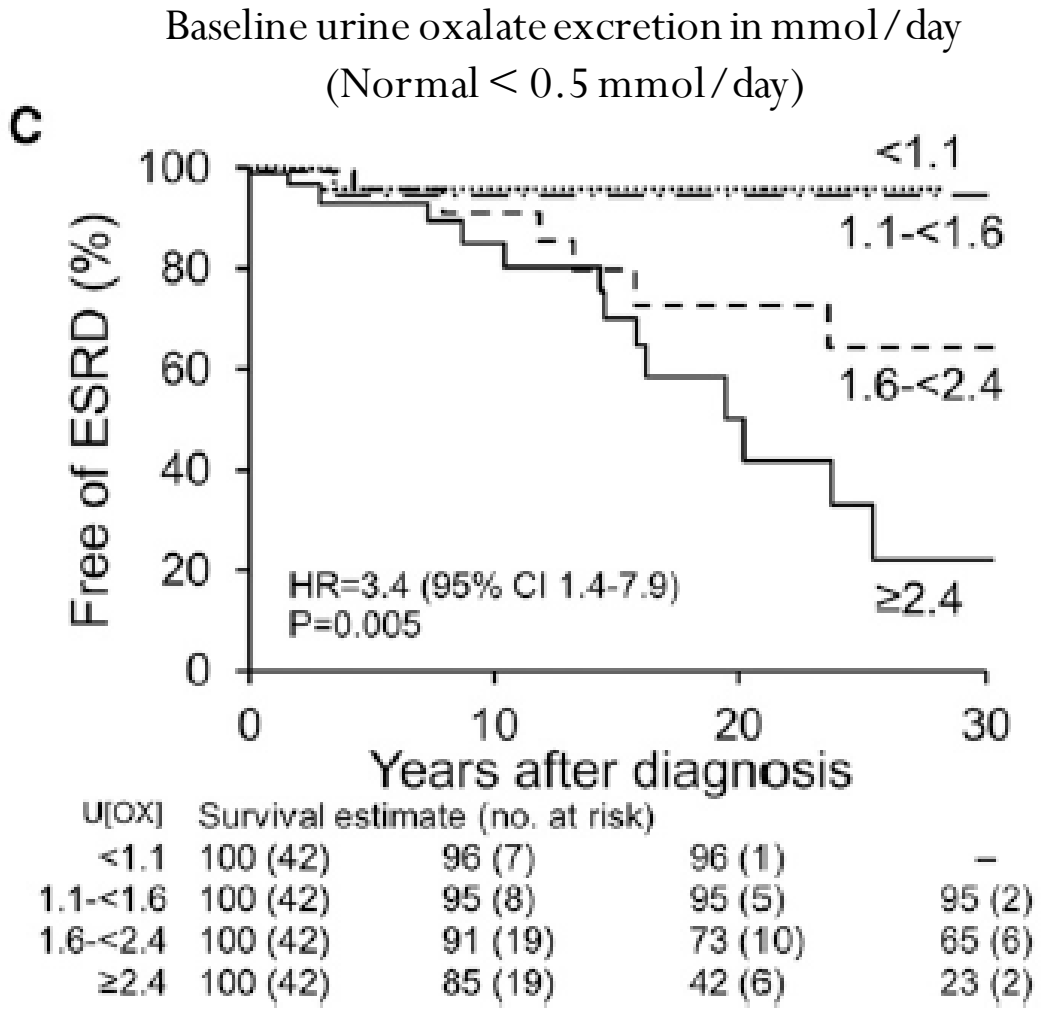
PH3 0





Zhao et al. CJASN 11:119, 2016, Rare Kidney Stone Consortium

Prognosis for renal survival among patients with Primary Hyperoxaluria



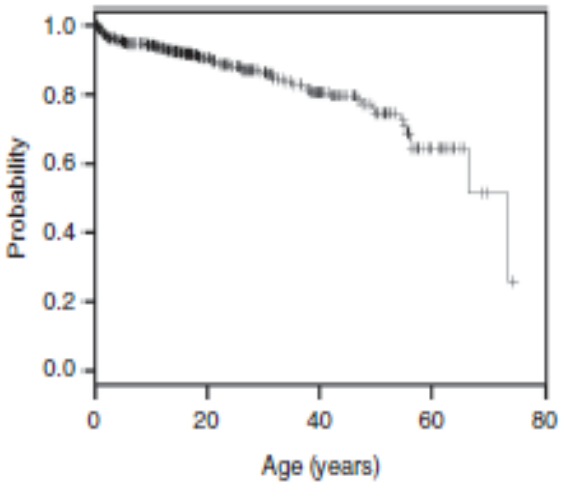
In PH patients who did not have ESRD at the time of diagnosis, prognosis was related to oxalate excretion.

Mortality is much higher in patients with ESRD

Zhao et al CJASN 2016

Outcome of PH1 correlates with AGXT mutation type

Patient survival in the OxalEurope Cohort (n=526)



Age at ESRD was higher for Those with at least one Mutated G170R allele

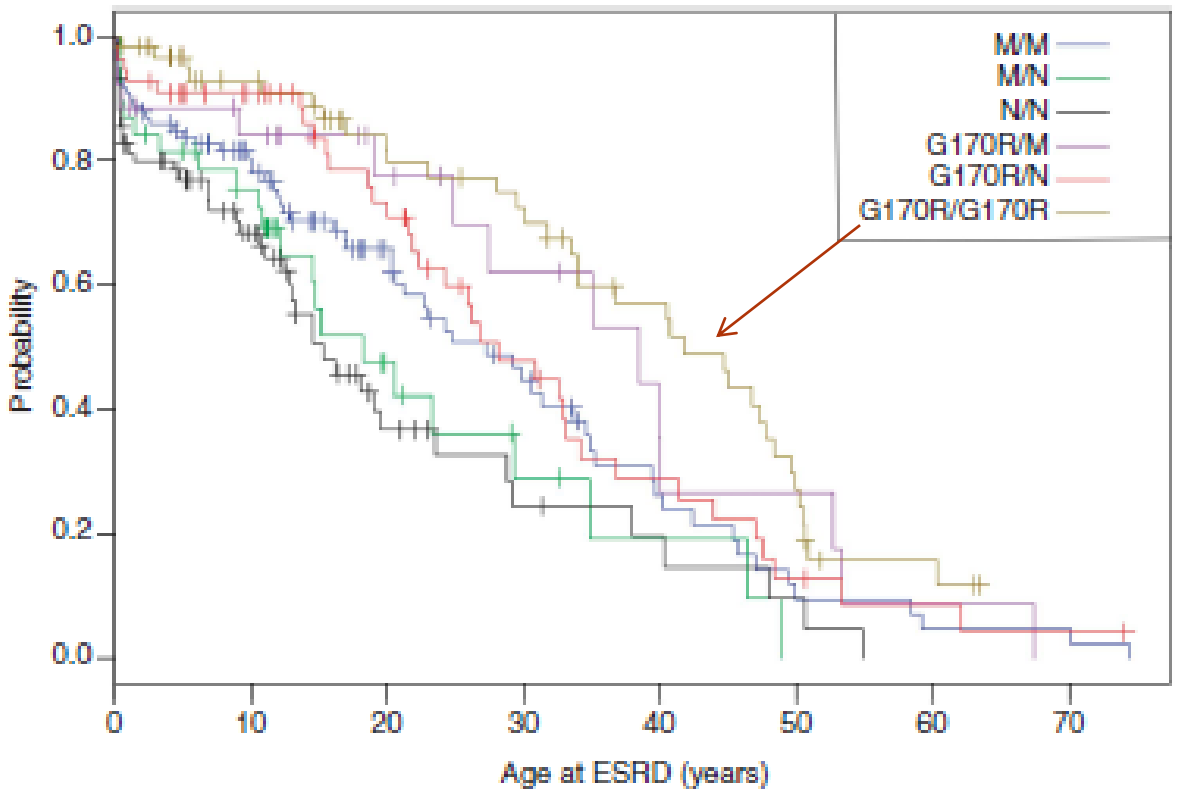


Figure 2 | Censored Kaplan–Meier curves for age at onset of end-stage renal disease (ESRD) for each genotype class. Data were available for 355 patients; log-rank test *P*-value <0.001.

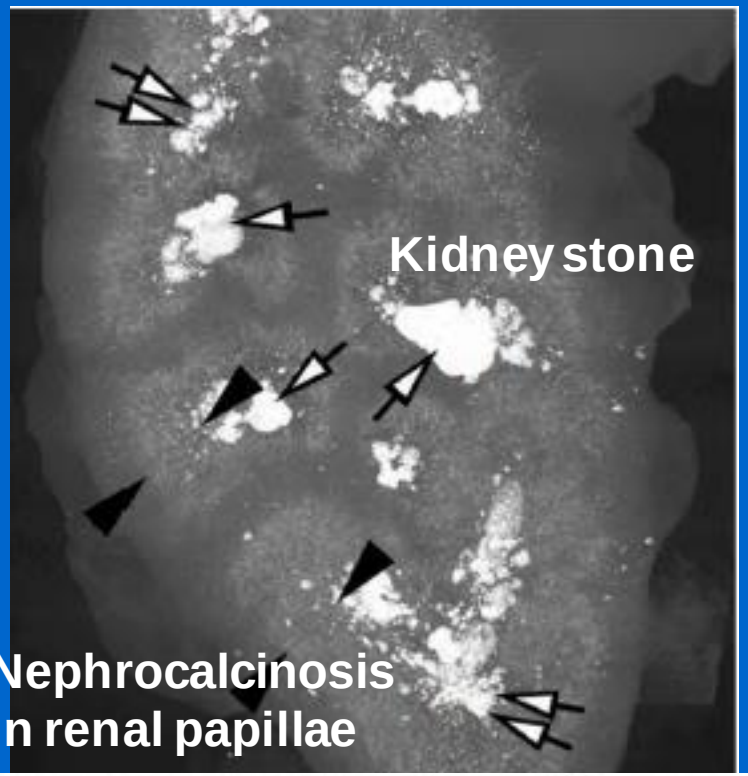
Mandrile et al KI 86:1197, 2014

Organ involvement by oxalosis in PH1 with kidney failure

Oxalosis occurs when oxalate excretion by the kidney cannot keep up with production

Frequency	Organ	Symptoms
Always	Kidney	Stones, nephrocalcinosis
Frequent	Bone	Fractures, bone pain, poor growth
	Eyes	Vision loss
Often	Arteries	Calcification
	Heart	Heart failure, abnormal rhythm, enlargement
	Thyroid	Hypothyroidism
Occasional	Skin, nerves, muscle, bowel, joints	

Native kidney from patient with PH1 and ESRD, removed at time of transplant

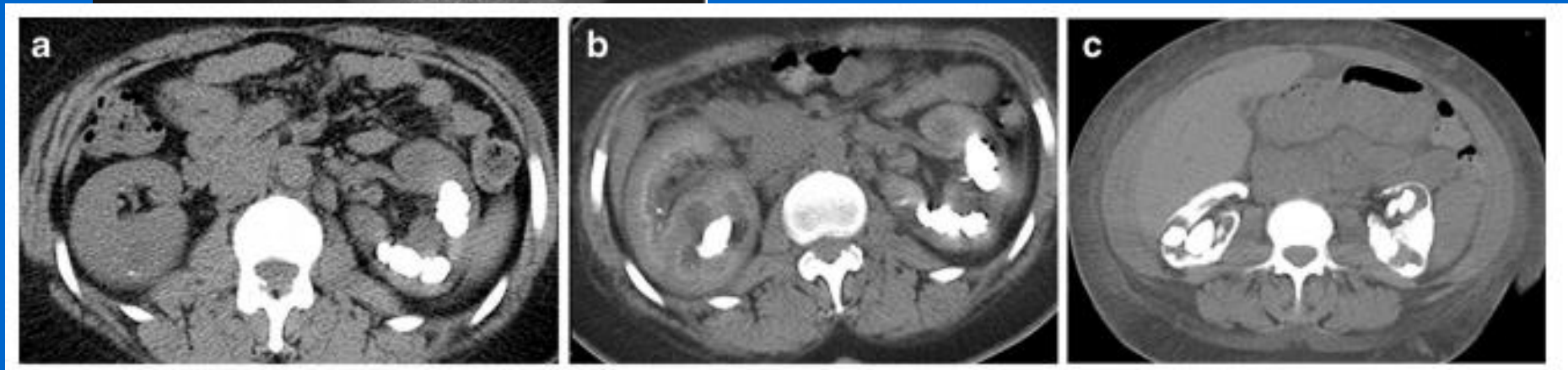


CT scan of kidney from 56 yr old man with PH1 on dialysis for 2 months

First stone – age 37
PH1 diagnosis – age 47
ESRD – age 56
History of > 20 stones

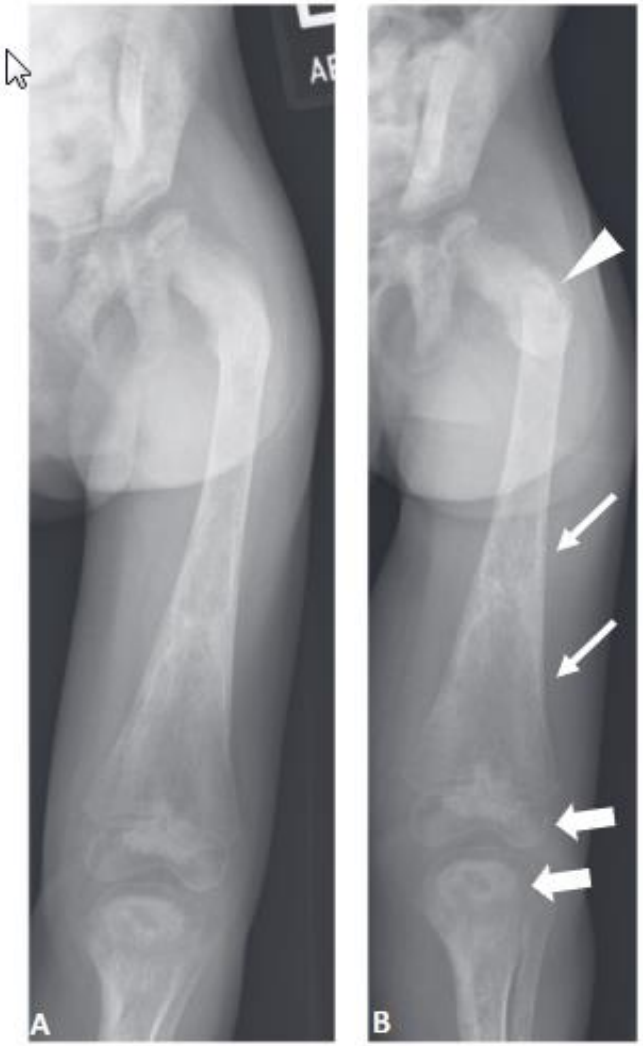
Strauss Ped Rad 2017
Worcester AJP Renal 2013

34 y/o F with PH1- CT progression 3 yrs

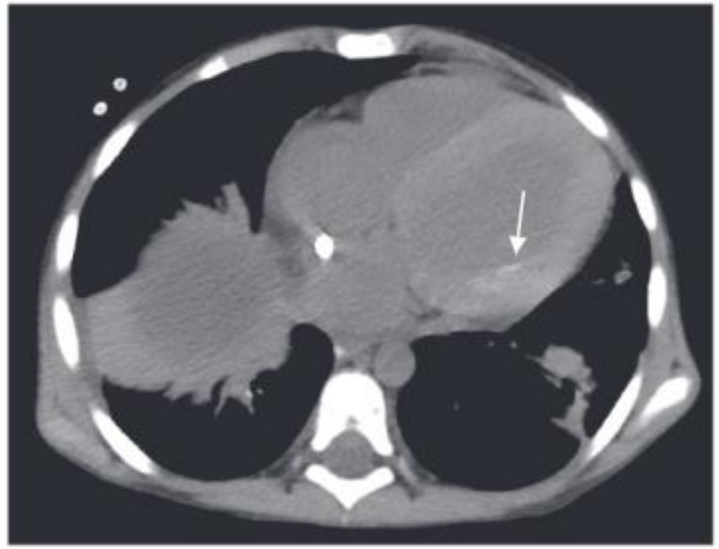


Oxalosis in Primary Hyperoxaluria

Femur of 3 year old child with followup three days later showing pathologic fracture



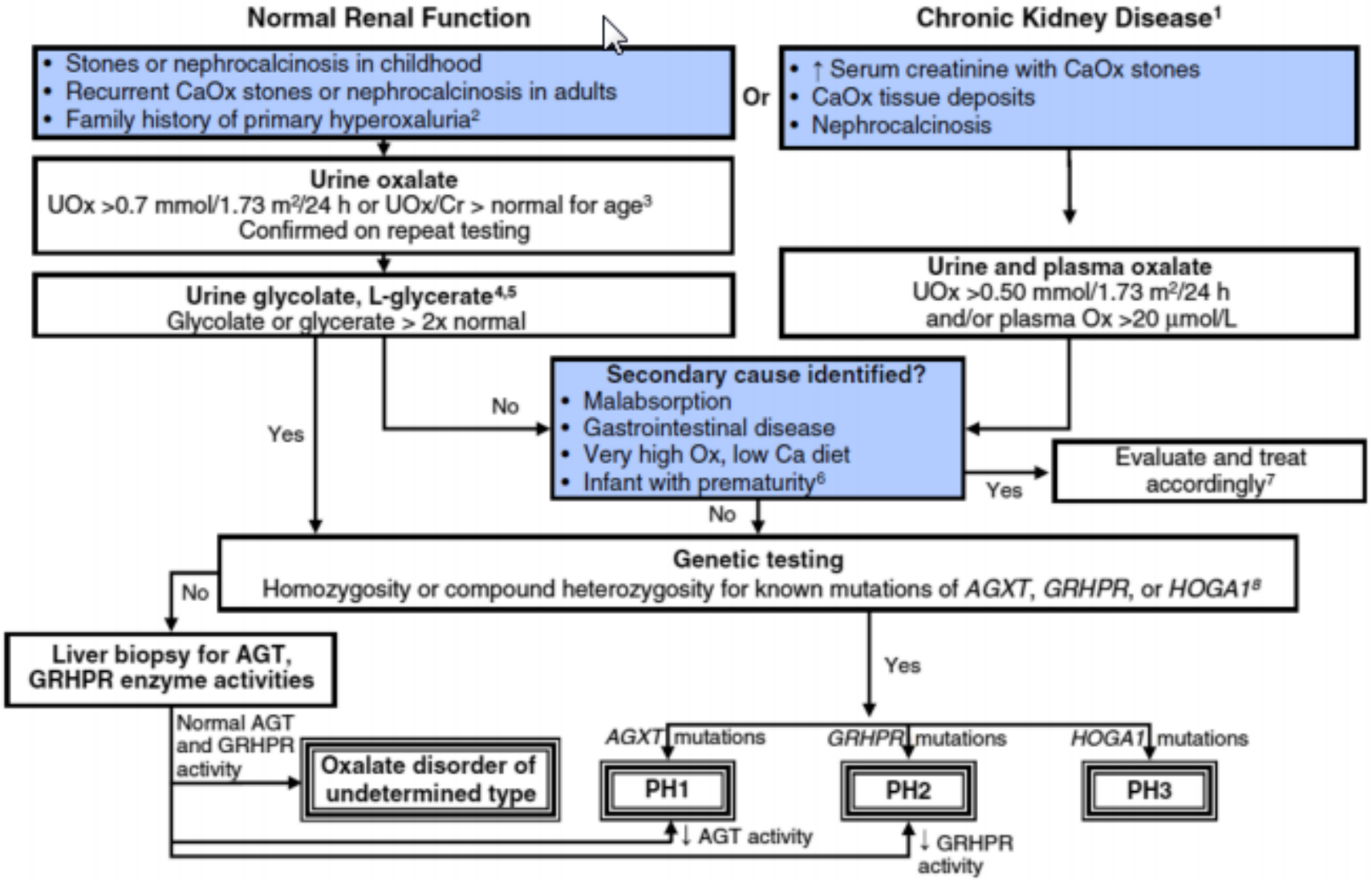
Calcification in the heart



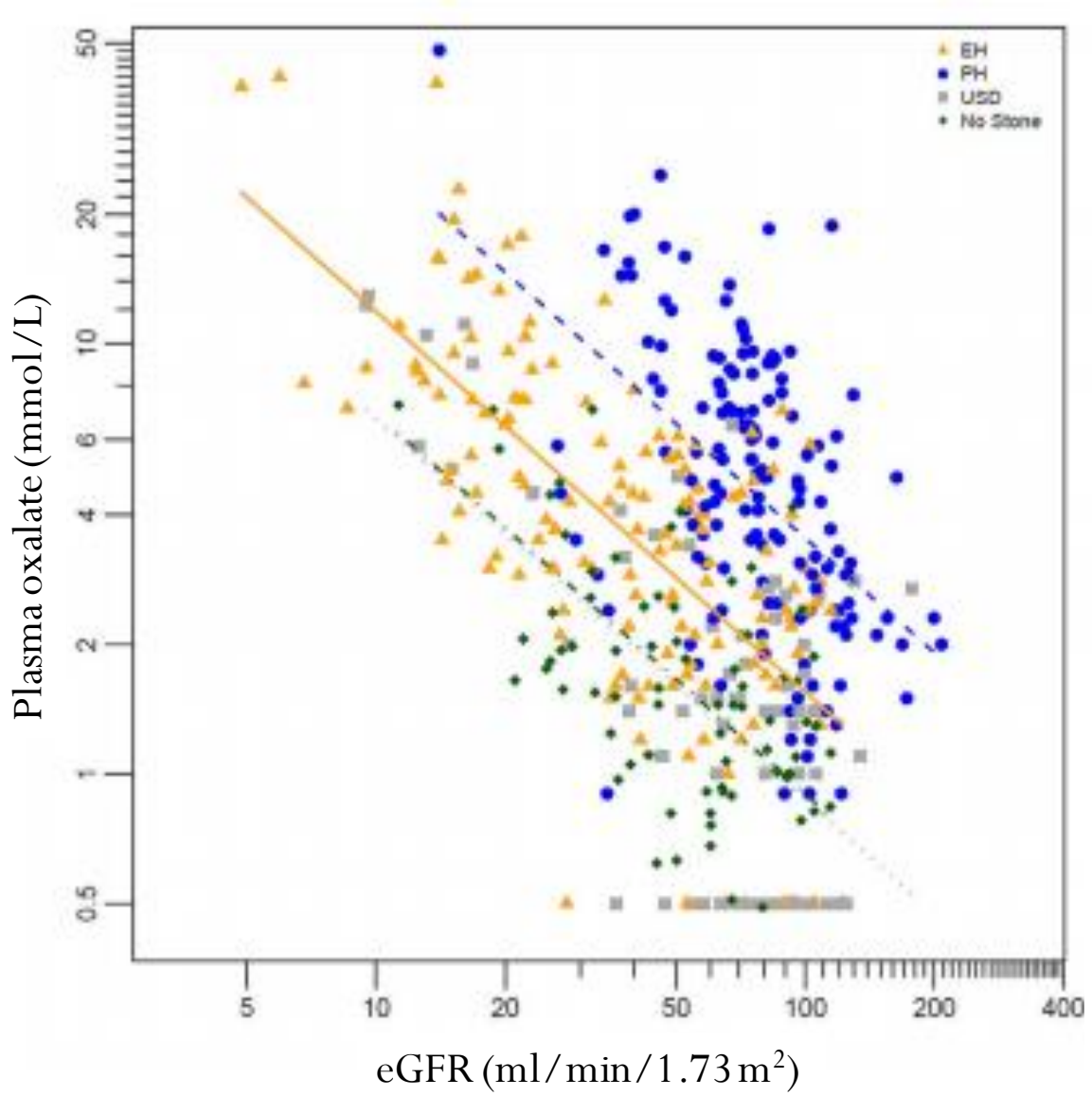
Calcifications in blood vessels

Rootman et al Clinical Imaging 2018

Diagnosis of Primary Hyperoxaluria



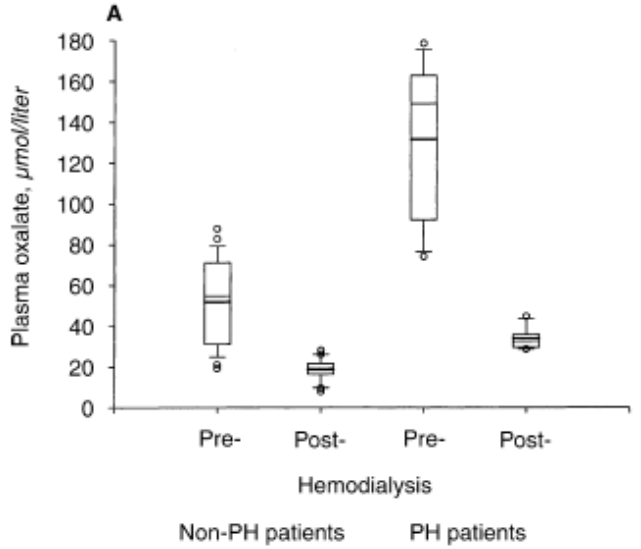
Sas, Harris, Milliner Urolithiasis 2019



Relationship between eGFR and plasma oxalate

- No stones
- Idiopathic stones
- Enteric hyperoxaluria
- Primary hyperoxaluria

Effect of dialysis on serum oxalate



Perinpam et al, Clin Biochem 2017
Hoppe et al KI 1999

Current treatment

- Hydration – goal to achieve fluid intake of 4 liters/day in adults, 2-3 liters in children, 1-1.5 in infants (may require placement of gastrostomy tube)
- Prompt treatment for vomiting or diarrhea, avoid salt depletion
- Crystallization inhibitors:
  - Citrate – 30-60 meq/day in adults
  - Orthophosphate
- Pyridoxine in patients with responsive mutations
- Use of endoscopic techniques for stone removal
- Renal replacement therapy and transplant
  - Combined liver and kidney, or sequential liver then kidney

    Patient survival after LKT 74% at 10 years

Current problems

- Improve awareness of Primary Hyperoxaluria to allow earlier detection and treatment
- Aggressive management to decrease recurrent stones, which may also decrease crystal deposition in tissue that leads to renal failure
- Better treatments to prevent renal failure
- Better treatments to avoid systemic oxalosis

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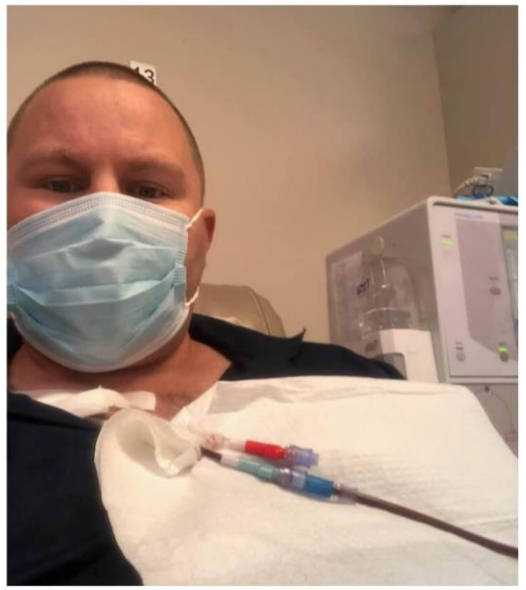
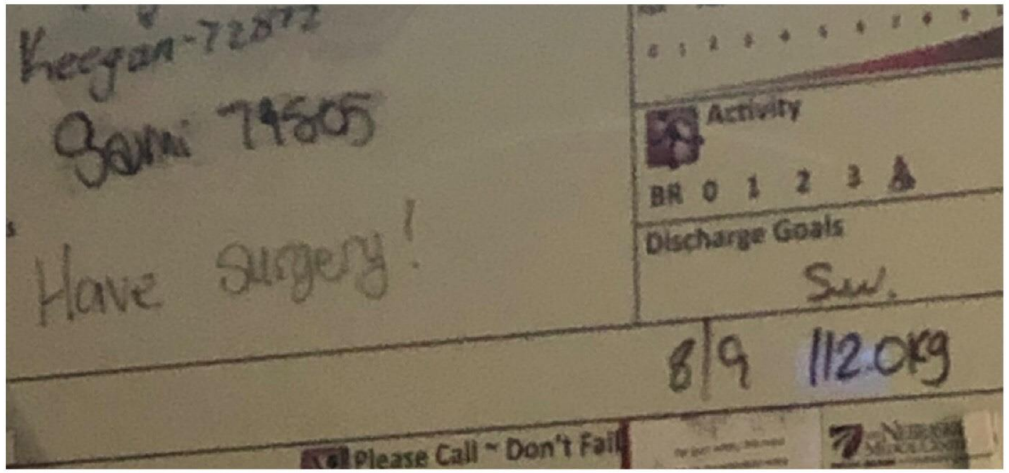
Q&A Session

Delay in diagnosis

Life on Dialysis April 2018-August 2019



Destination: Liver/Kidney Transplant Aug. 9th 2019



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Introduction

- Pritesh Gandhi, PharmD. – Vice President, General Manager, Lumasiran

Primary Hyperoxaluria Type 1 & Physician Perspective

- Elaine M. Worcester, M.D. – Nephrologist & Professor of Medicine, University of Chicago Medicine

Patient & Caregiver Perspective

- Andrew – Patient Diagnosed with Primary Hyperoxaluria Type 1
- Nicole – Andrew's Wife and Caregiver

Early Stage Clinical Data & ILLUMINATE Studies

- Kenji Fujita, M.D. – Vice President, Clinical Development

Lumasiran Program Opportunity in PH1 & Disease Education/Diagnosis Initiatives

- Pritesh Gandhi, PharmD. – Vice President, General Manager, Lumasiran

Q&A Session

Lumasiran

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

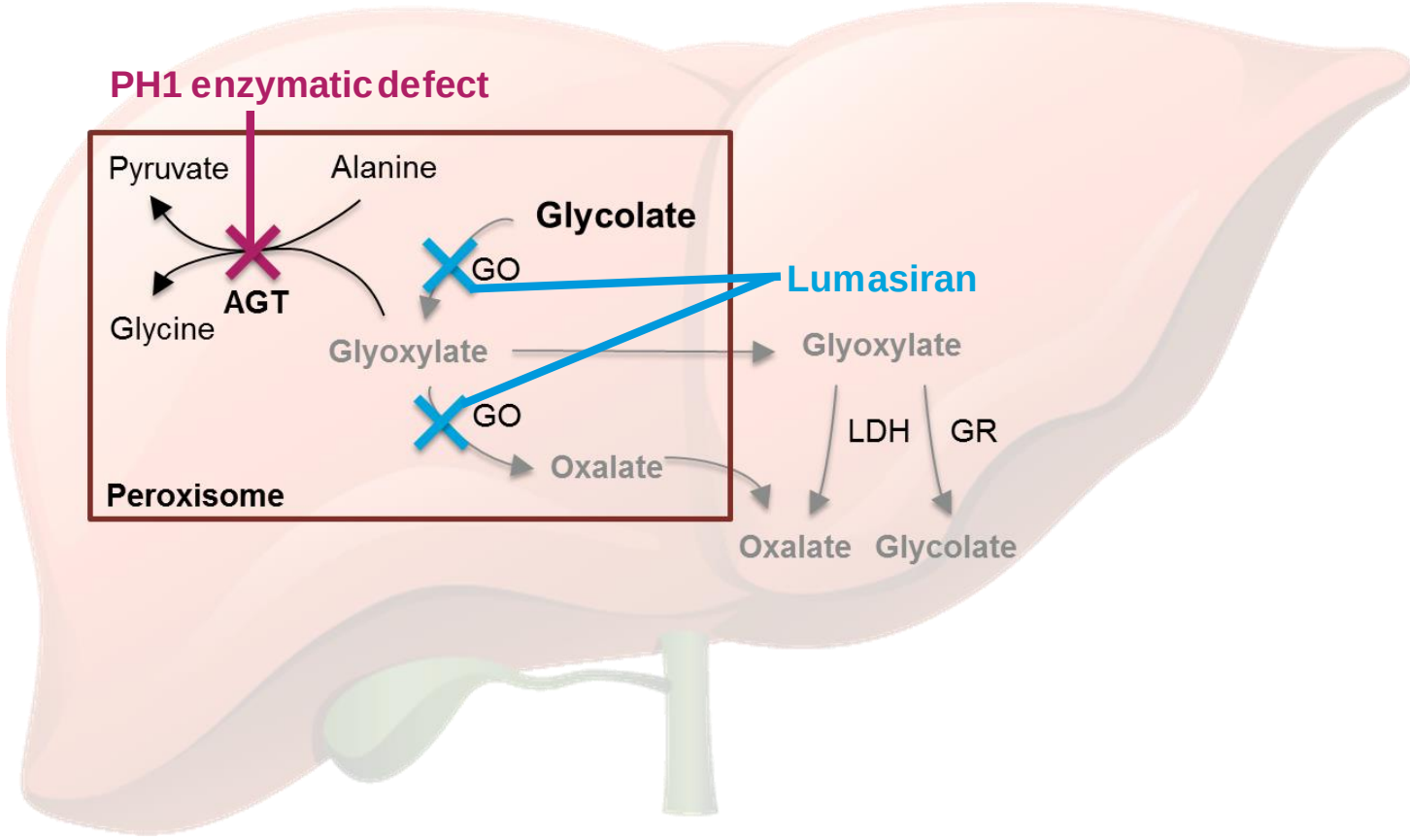
Lumasiran (ALN-GO1):

- 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.

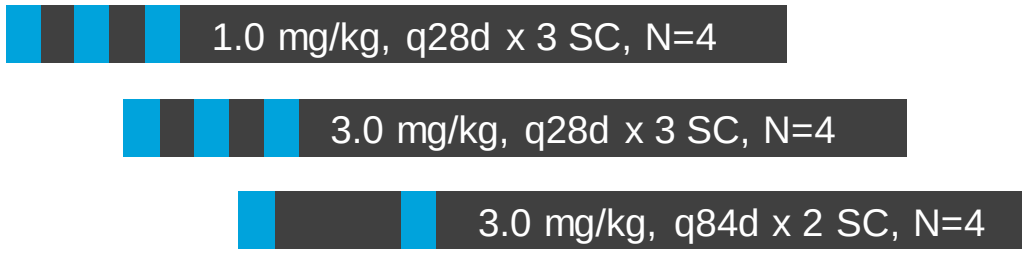
HAO1, hydroxyacid oxidase 1

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

Lumasiran Phase 1/2 Study†

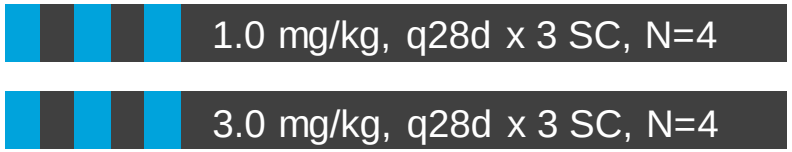
Study Design & Demographics: Part B (Patients with PH1)

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



Patients randomized to placebo received subsequent dosing of lumasiran

Expansion Cohorts | Open-label



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)

T. McGregor, presented at the 2019 Oxalosis & Hyperoxaluria (OHF) International Workshop, Boston, MA, 22 June 2019
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

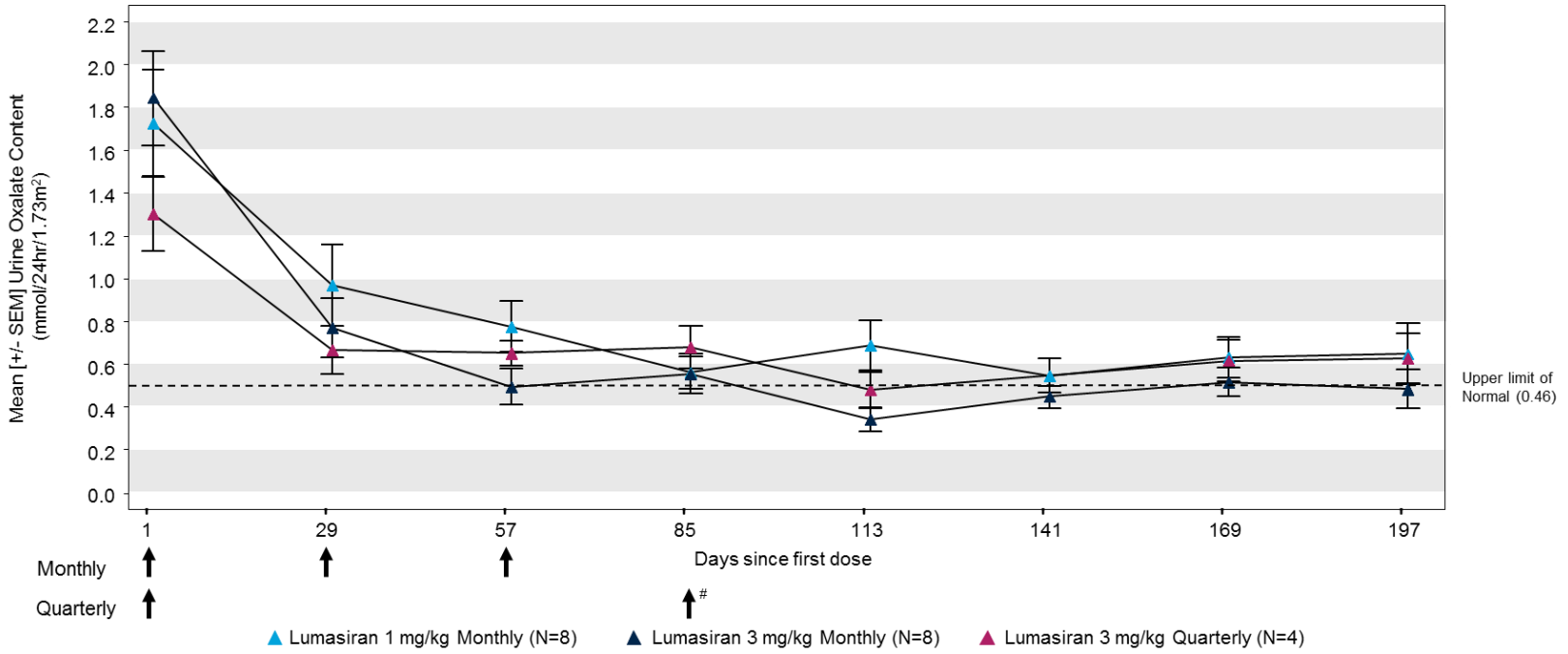
T. McGregor, presented at the 2019 Oxalosis & Hyperoxaluria (OHF) International Workshop, Boston, MA, 22 June 2019
SAE, serious adverse event

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

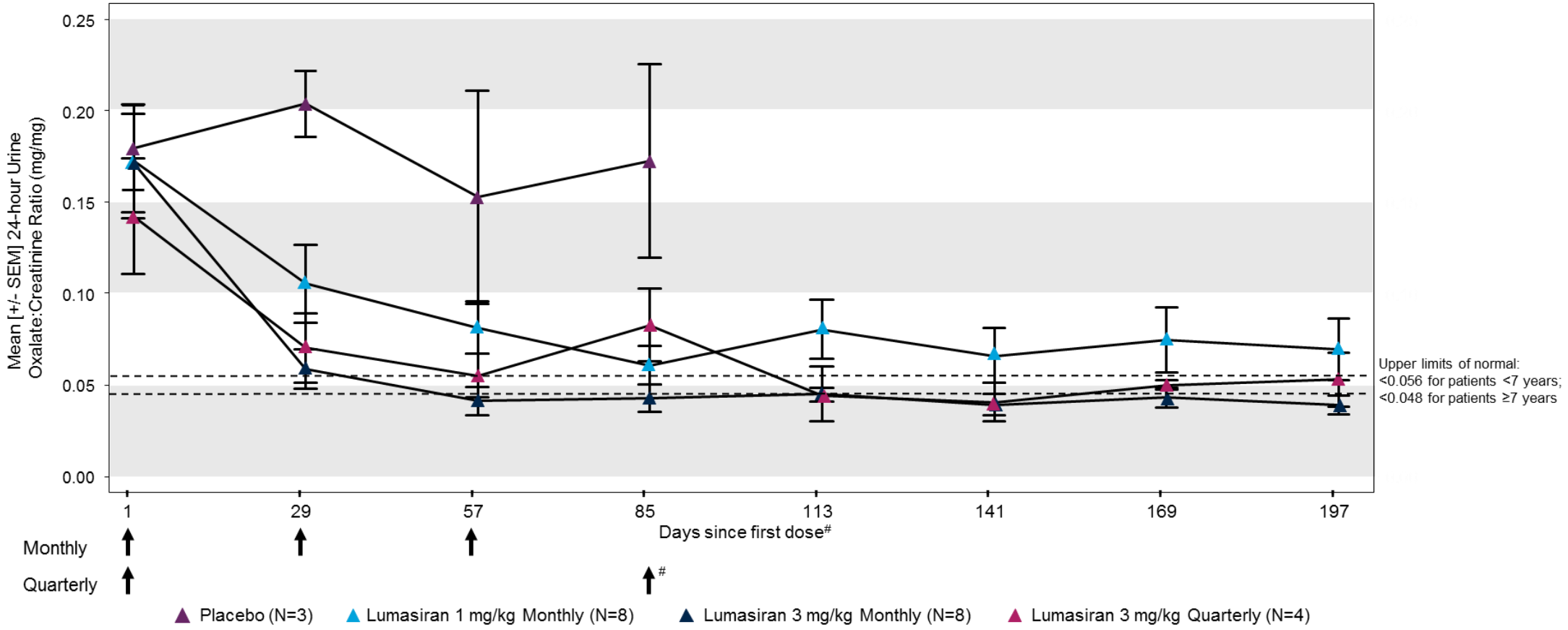


T. McGregor, presented at the 2019 Oxalosis & Hyperoxaluria (OHF) International Workshop, Boston, MA, 22 June 2019
Only data points with at least 3 contributing patients are represented.
†Patients who had a valid 24-hour urinary oxalate assessment; placebo data not shown due to limited valid collections
‡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)



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Lumasiran Phase 1/2 and Phase 2 OLE

Study Design

- **Patients previously dosed in Phase 1/2† study eligible to enroll into Phase 2^ open-label extension (OLE) study**
  - All patients completed follow-up in Phase 1/2 have enrolled in OLE (N=20)
    - Data presented here represent 18 patients dosed in Phase 2 OLE, as of 8 Feb 2019
      - Preliminary efficacy data of urinary oxalate and urinary oxalate/creatinine ratio includes 9 and 10 patients, respectively, who have reached Day 85
  - Patients have been on study for a median of 4 months (range: 0.03–8.36; N=18)

Phase 1/2 Part B – Patients with PH1 (N=20)

- 1.0 mg/kg, q28d x 3 SC, N=8
- 3.0 mg/kg, q28d x 3 SC, N=8
- 3.0 mg/kg, q84d x 2 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

Phase 2 OLE (N=18)

- 1.0 mg/kg, q28d SC, N=3
- 3.0 mg/kg, q28d SC, N=6
- 3.0 mg/kg, q84d SC, N=9

- Doses listed are the initial dose patients received in the Phase 2 OLE
- Patients were started at their original dose from the Phase 1/2 study unless different dose approved prior to dosing

T. McGregor, presented at the 2019 Oxalosis & Hyperoxaluria (OHF) International Workshop, Boston, MA, 22 June 2019

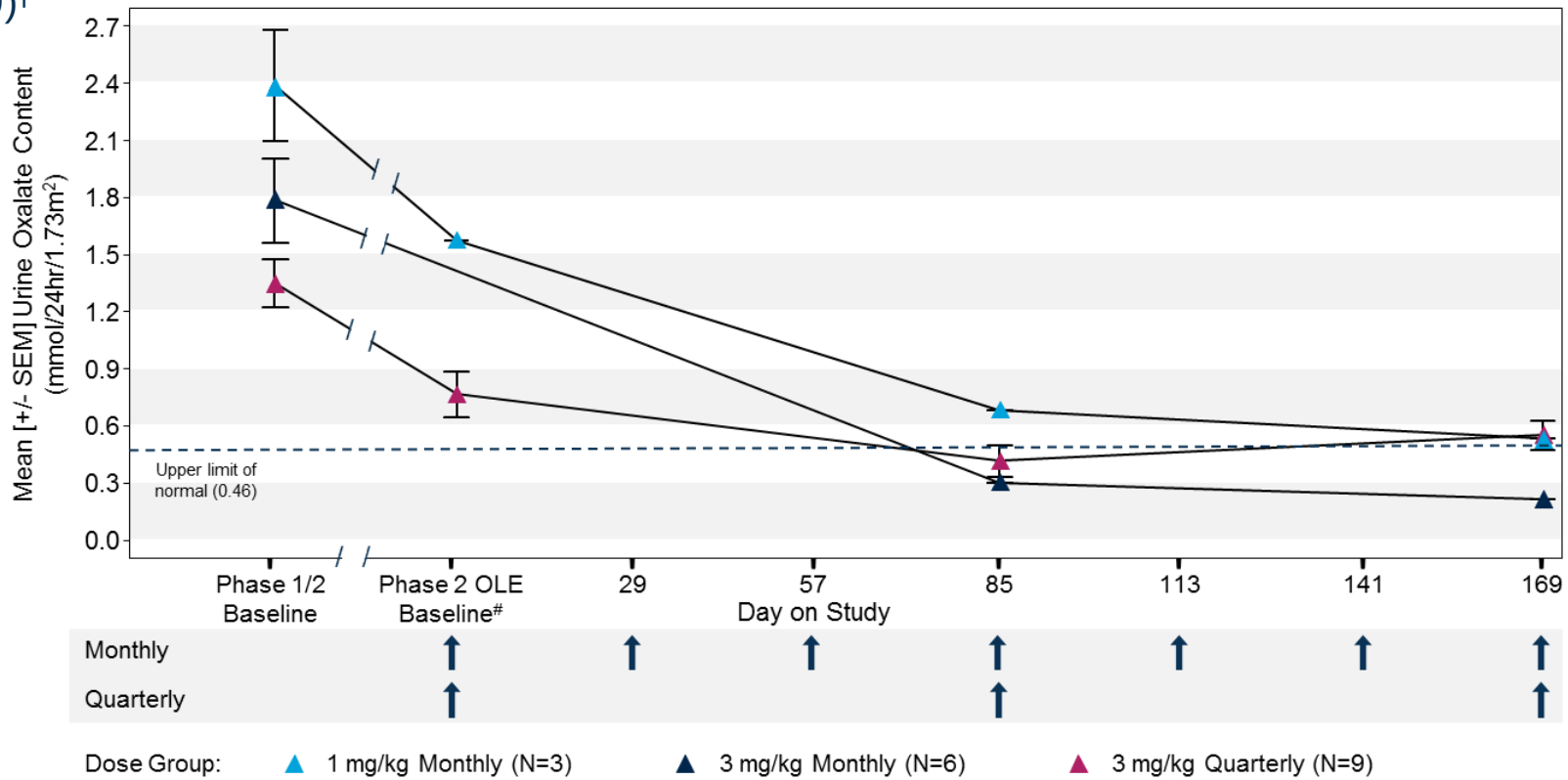
†ClinicalTrials.gov Identifier: NCT02706886; EudraCT Number: 2015-004407-23; ^ClinicalTrials.gov Identifier: NCT03350451; EudraCT Number: 2016-003134-24

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)†



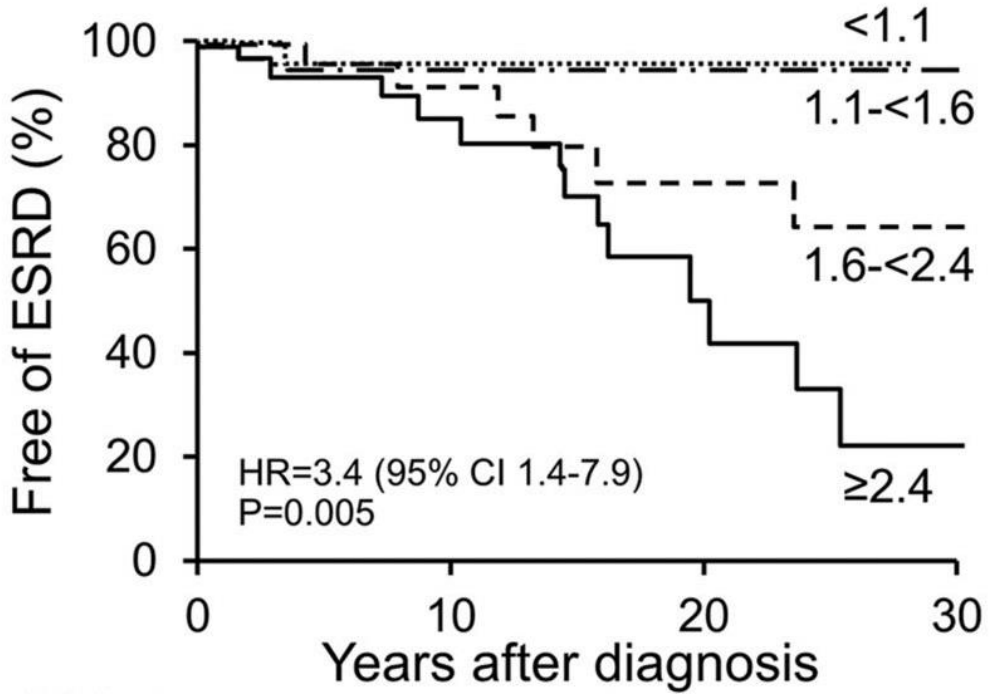
T. McGregor, presented at the 2019 Oxalosis & Hyperoxaluria (OHF) International Workshop, Boston, MA, 22 June 2019

*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

Potential Significance of Decreasing Urinary Oxalate

In the Phase 1/2 Study, lumasiran lowered UOx below 1.1 mmol/24hr/1.73m^2 in all patients with baseline excretion ≥ 1.6 mmol/24hr/1.73m^2



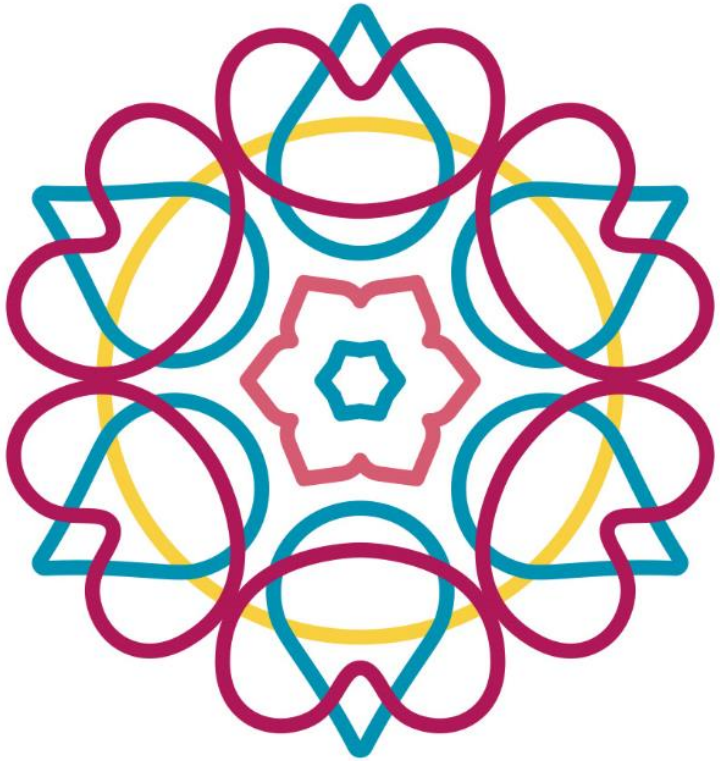
- Renal survival was examined by quartile of urine oxalate (UOx) excretion (mmol/24hr/1.73m2) at diagnosis in patients with any form of PH. Among patients with PH who did not have ESRD at diagnosis, renal survival estimates were lower in those with highest level of urinary oxalate excretion.

Zhao et al. CJASN 2016;11:119-126

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

Lumasiran ILLUMINATE•A Phase 3 Study

Randomized, Double-Blind Study in Primary Hyperoxaluria Type 1 Patients

ENROLLMENT COMPLETED

Patient Population

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

2:1 RANDOMIZATION

Lumasiran
3xqM loading dose, then q3M
3.0 mg/kg SC†

or

Placebo
3xqM loading dose, then q3M SC

Primary Endpoint

- Percent change in urinary oxalate excretion from baseline (average percent change from baseline across months 3 through 6)

Open-Label Extension

ILLUMINATE•A

FDA Breakthrough and EMA PRIME Designations

Topline ILLUMINATE-A results expected in **late 2019**

NDA submission planned in **early 2020** (assuming positive results)

*NCT03681184; EudraCT Number: 2018-001981-40

† 3.0 mg/kg once monthly for 3 consecutive months (loading dose phase) followed by 3.0 mg/kg once every 3 months (maintenance phase) starting 1 month after last loading dose

Lumasiran ILLUMINATE•B Phase 3 Study

Open-Label Study in Pediatric Primary Hyperoxaluria Type 1 Patients

NOW ENROLLING
Patient Population (N=8)

- Infants and children <6 years
- Elevated urinary oxalate:creatinine ratio
- Confirmed alanine glyoxylate aminotransferase (AGXT) mutation
- eGFR >45 mL/min/1.73 m2 if ≥12 months old; non-elevated serum creatinine if <12 months old

Open-Label

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

Primary Endpoint

- Percent change in urinary oxalate excretion at 6 months (average percent change from baseline across months 3 through 6)

Open-Label Extension ‡

ILLUMINATE•B

FDA Breakthrough and EMA PRIME Designations

ILLUMINATE-C expected to initiate in **late 2019**

Topline ILLUMINATE-B results expected in **mid-2020**

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
ILLUMINATE-C: single-arm, open-label study in patients with impaired renal function

Lumasiran Registrational Program

Robust Registrational Program to Evaluate Lumasiran Across all Ages and Full PH1 Disease Spectrum

ILLUMINATE-A

Double-blind, placebo-controlled trial in PH1 patients at least 6 years old with preserved renal function

ILLUMINATE-B

Single arm, open-label study in PH1 patients less than 6 years old with preserved renal function

ILLUMINATE-C

Single arm, open-label study in PH1 patients with impaired renal function

- **Expanded Access Protocol (EAP) for PH1 patients at least 6 years old with preserved renal function recently approved in U.S.**

Alnylam® PHARMACEUTICALS

Agenda

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Lumasiran Market Opportunity

Ultra-Rare Orphan Disease with Potential First-in-Class/Best-in-Class Medicine

PREVALENCE	DIAGNOSIS	DISEASE BURDEN	COST BURDEN
~3–5K	**~50%**	**30–65%**	**$1M+**
patients in U.S./EU[1]	currently diagnosed[2]; mean time to diagnosis ~6 years[3]	reach end-stage renal disease before diagnosis[3]	average cost (transplant & lifelong immunosuppression)

LUMASIRAN | PRIMARY HYPEROXALURIA TYPE 1

>$500M potential market opportunity

[1] Cochat P, et al. N Engl J Med. 2013;369:649-658
[2] Hopp R, et al. J Am Soc Nephrol. 2015;26:2559-2570
[3] Harambat J, et al. Kidney Int. 2010;77(5):443-449

Launch of Children's Animation Video Series for PH1

Learn more at ph1ofakind.com

- First-of-its-kind animated video series for kids about kids living with PH1; fills a significant gap in educational content for young patients
- 4-part video series and additional content in development; 1st video debuted in early Sept; remaining videos by EOY
- Enthusiastic reception from PH1 community
- Developed in partnership with the Oxalosis & Hyperoxaluria Foundation (OHF)

"The emotions children experience when diagnosed with PH1 can be overwhelming. Many parents are left searching for ways to explain what's going on to not only their small children, but also the people who make up their support system. I'm so excited to see PH1 of a Kind come to life – it will be an incredibly valuable resource that this community so very much needs and deserves."

- Kim Hollander – Executive Director, OHF

Increasing PH1 Awareness

Education Initiatives Developed for Physicians

Alnylam Act® – Primary Hyperoxaluria Type 1

No-Charge, Third-Party Genetic Testing and Counseling Program

Reduce barriers to genetic testing and counseling to help people make more informed decisions about their health

Tests and services are performed by independent third parties

Available in U.S. and Canada (genetic counseling service available in U.S.)

Healthcare professionals who use this program have **no obligation** to recommend, purchase, order, prescribe, promote, administer, use or support any Alnylam product*

More information regarding this program available at: **www.alnylamact.com**

*At no time does Alnylam receive patient-identifiable information. Alnylam receives contact information for healthcare professionals who use this program.

Potential Timeline for Initial Approval

U.S. and E.U.
2020

ROW
2022+

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Q&A Session

SAVE THE DATE

Alnylam R&D Day

Friday, November 22, 2019

Westin Times Square
New York City

Alnylam® PHARMACEUTICALS

CHALLENGE ACCEPTED

Alnylam PHARMACEUTICALS