



Claire, 10, living with PH1

Lumasiran, in Development for the Treatment of Primary Hyperoxaluria Type 1 (PH1)

August 15, 2018



Agenda

Welcome

- Josh Brodsky, Director, Investor Relations & Corporate Communications

Introduction

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

Overview of Primary Hyperoxaluria Type 1

- Sally-Anne Hulton, M.D., FRCPCH, MRCP, FCP, MBBCh, Consultant Paediatric Nephrologist and Clinical Lead, Birmingham Children's Hospital NHS Trust

Patient Advocacy: Hyperoxaluria Patient Perspective

- Kim Hollander, Executive Director, Oxalosis & Hyperoxaluria Foundation

Lumasiran Program: Clinical Data and Next Steps

- Richard Riese, M.D., Ph.D., Vice President, Clinical Development
- 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; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; 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; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally; our ability to successfully expand the indication for ONPATPRO in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; 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 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. 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

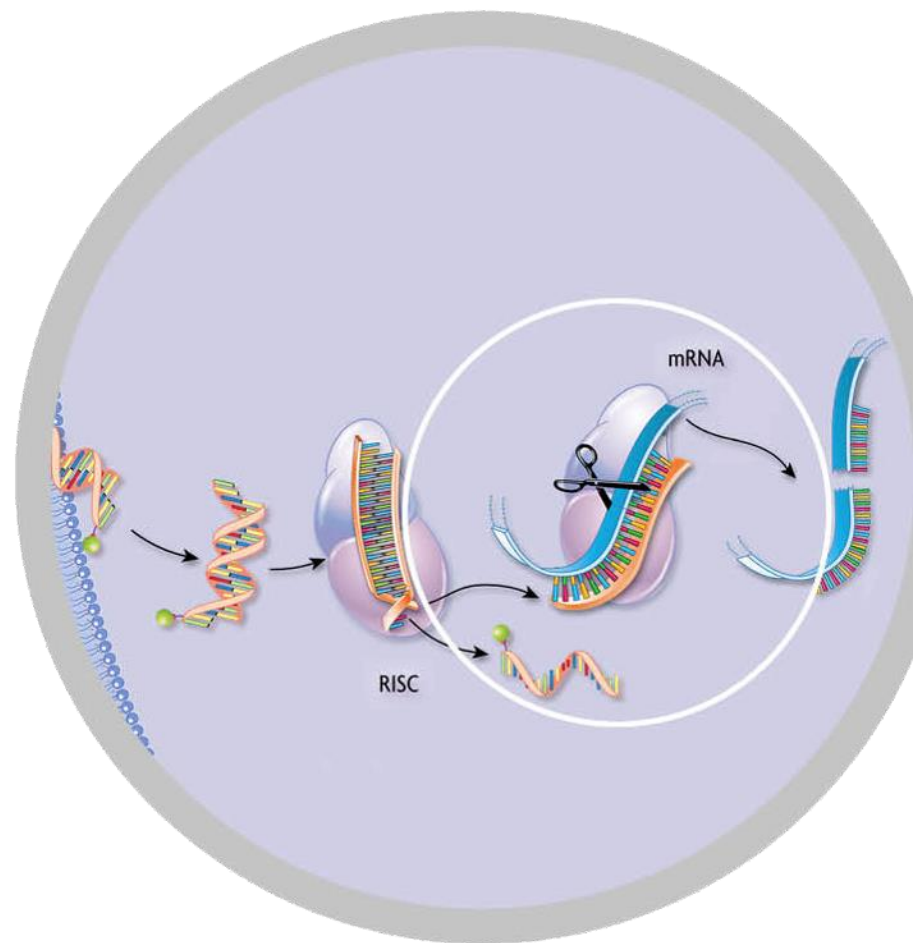
Nobel Prize-winning science

Silence any gene in genome

Potent and durable mechanism of action

Product engine for sustainable pipeline

Now commercial



The first RNAi therapeutic is
NOW APPROVED



onpattroTM
(patisiran) lipid complex
injection

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArS):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Hepatic Infectious Diseases
- CNS Diseases

		HUMAN POC ¹	BREAKTHROUGH DESIGNATION	EARLY STAGE (IND or CTA Filed-Phase 2)	LATE STAGE (Phase 2-Phase 3)	REGISTRATION	COMMERCIAL	COMMERCIAL RIGHTS
ONPATTRO™ (patisiran)²	<i>Polyneuropathy of Hereditary ATTR Amyloidosis</i>						●	Global
Givosiran	<i>Acute Hepatic Porphyrias</i>				●			Global
Fitusiran	<i>Hemophilia and Rare Bleeding Disorders</i>				●			15-30% Royalties
Inclisiran	<i>Hypercholesterolemia</i>				●			Milestones & up to 20% Royalties
ALN-TTRsc02	<i>ATTR Amyloidosis</i>			●				Global
Lumasiran	<i>Primary Hyperoxaluria Type 1</i>			●				Global
Cemdisiran	<i>Complement-Mediated Diseases</i>			●				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.

Anylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArS):

- Genetic Medicines
- Cardio-Metabolic Diseases
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- CNS Diseases

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Lumasiran for Primary Hyperoxaluria Type 1 (PH1)

Rationale for RNAi Therapeutic



1

Genetically validated, liver-expressed target gene

Lumasiran is designed to reduce hepatic levels of **glycolate oxidase (GO)**, thereby depleting substrate necessary for oxalate production, which directly contributes to pathophysiology of PH1.



2

Biomarker for POC in Phase 1

Urinary biomarkers:

- **glycolate**
- **oxalate**



3

Definable path to approval and market

Single pivotal study in PH1 patients (N~25)

Primary endpoint:

- Reduction in urinary oxalate relative to placebo at 6 months

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Primary Hyperoxaluria

Sally-Anne Hulton*

Birmingham Children's Hospital UK

Enzyme deficiency in the liver targets the kidneys

AGT enzyme
defect in the
liver → ↑
oxalate
production



Kidneys
normally excrete
oxalate

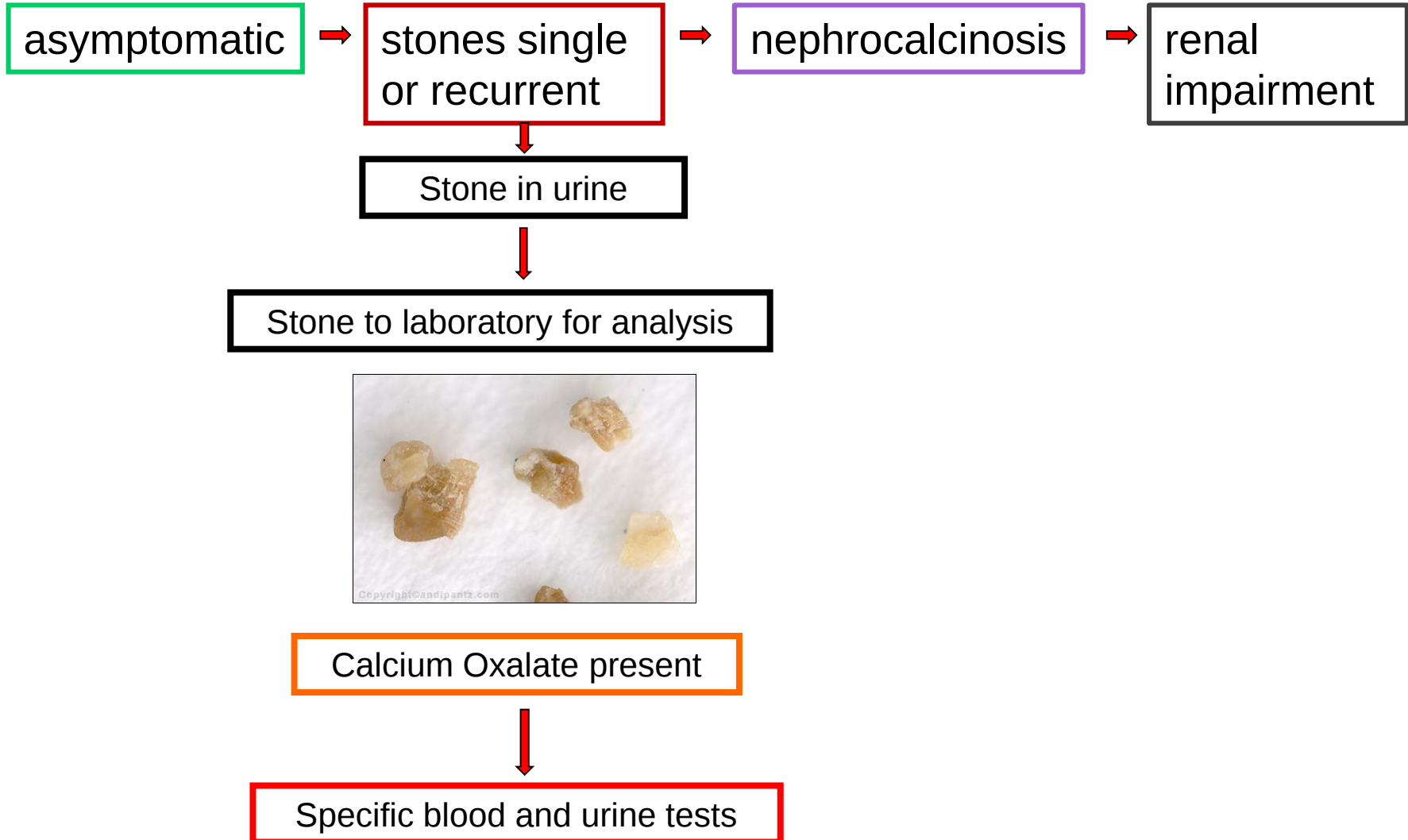
Oxalate deposits in kidneys forming stones +
calcification within the kidney (nephrocalcinosis)
resulting in kidney failure



As the kidneys fail, oxalate accumulates in the blood vessels to all organs of the body with effects known as **systemic oxalosis**

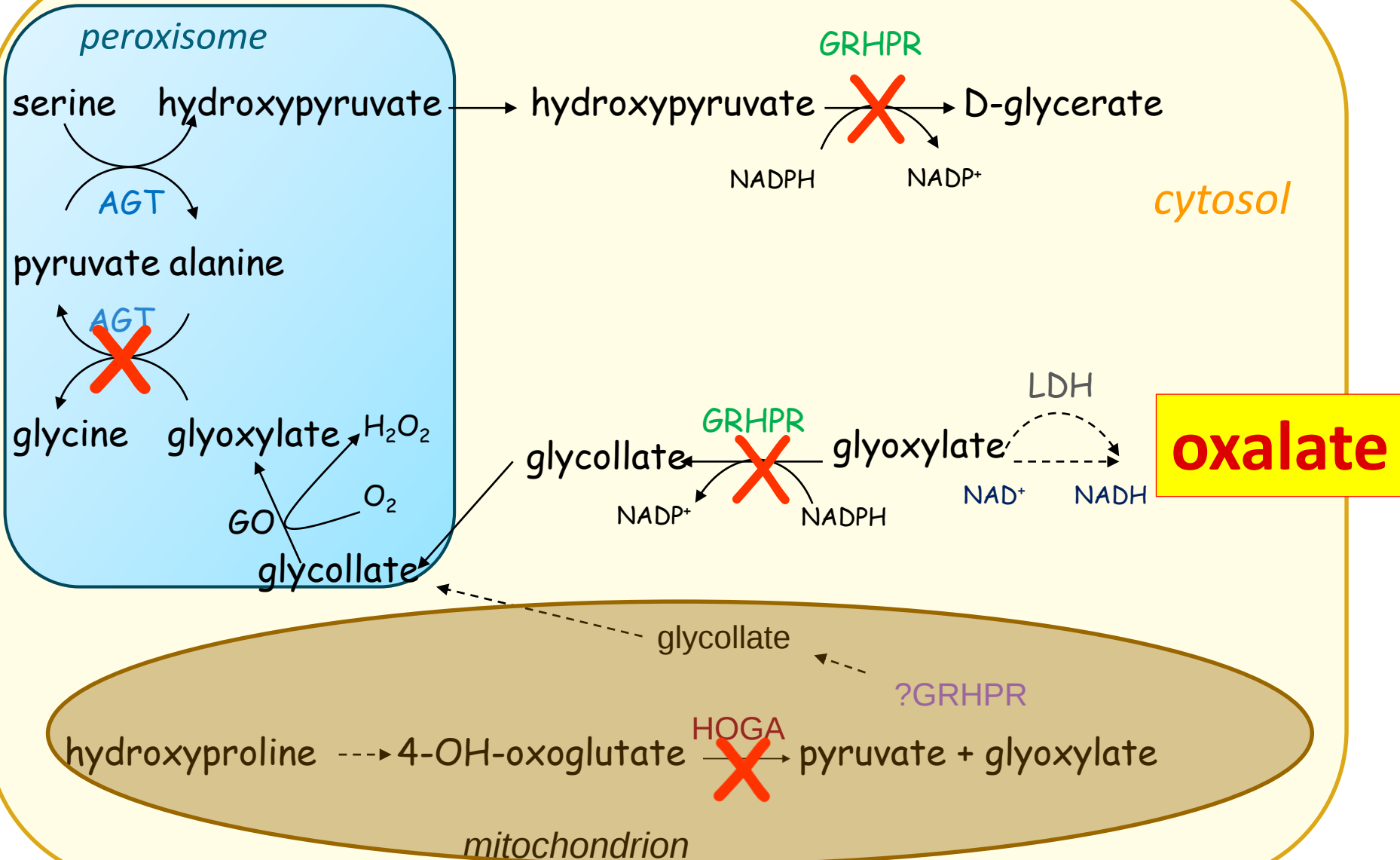


Clinical presentation & diagnosis





Oxalate Synthesis

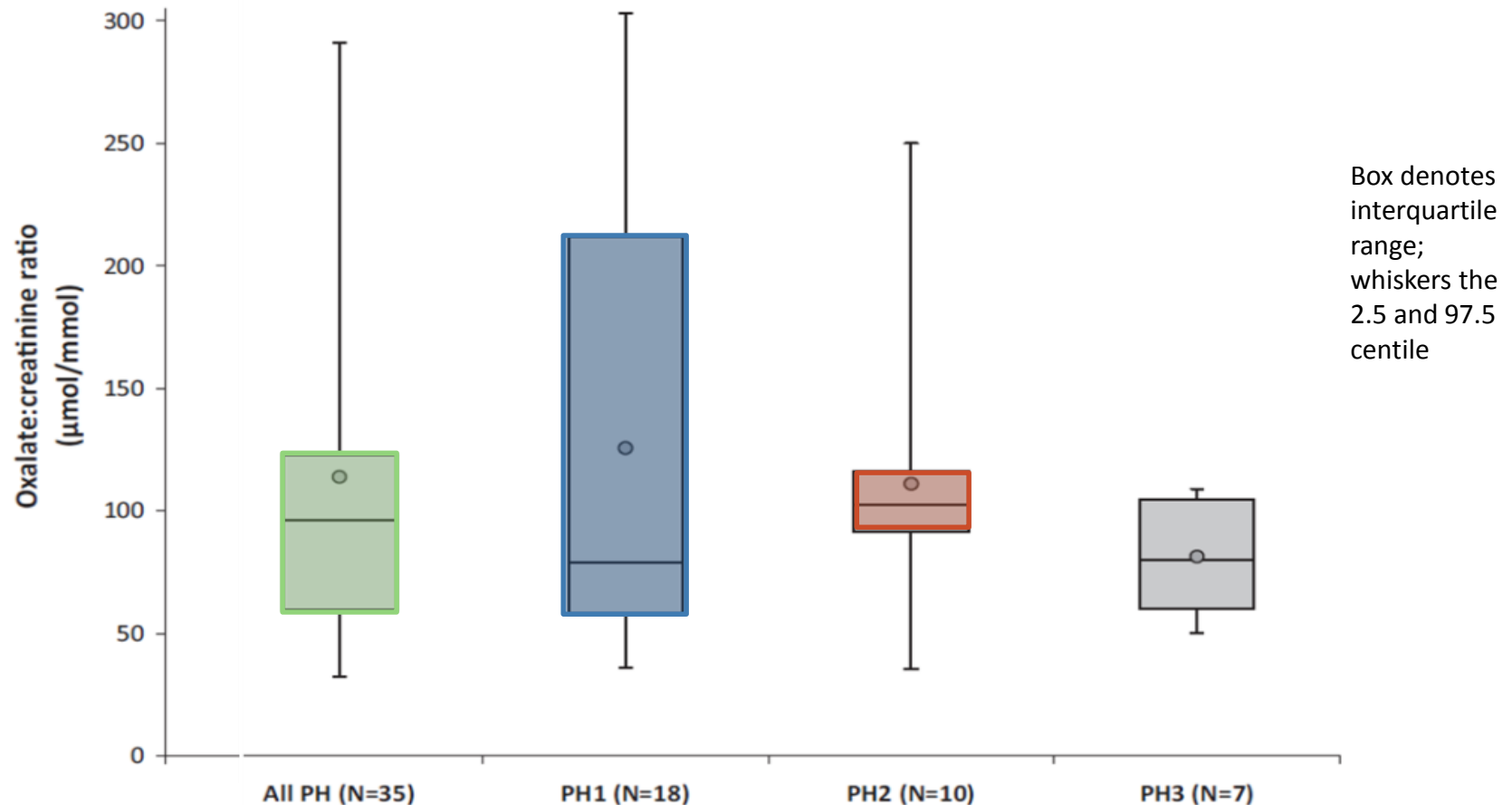


PH mutations & diagnosis

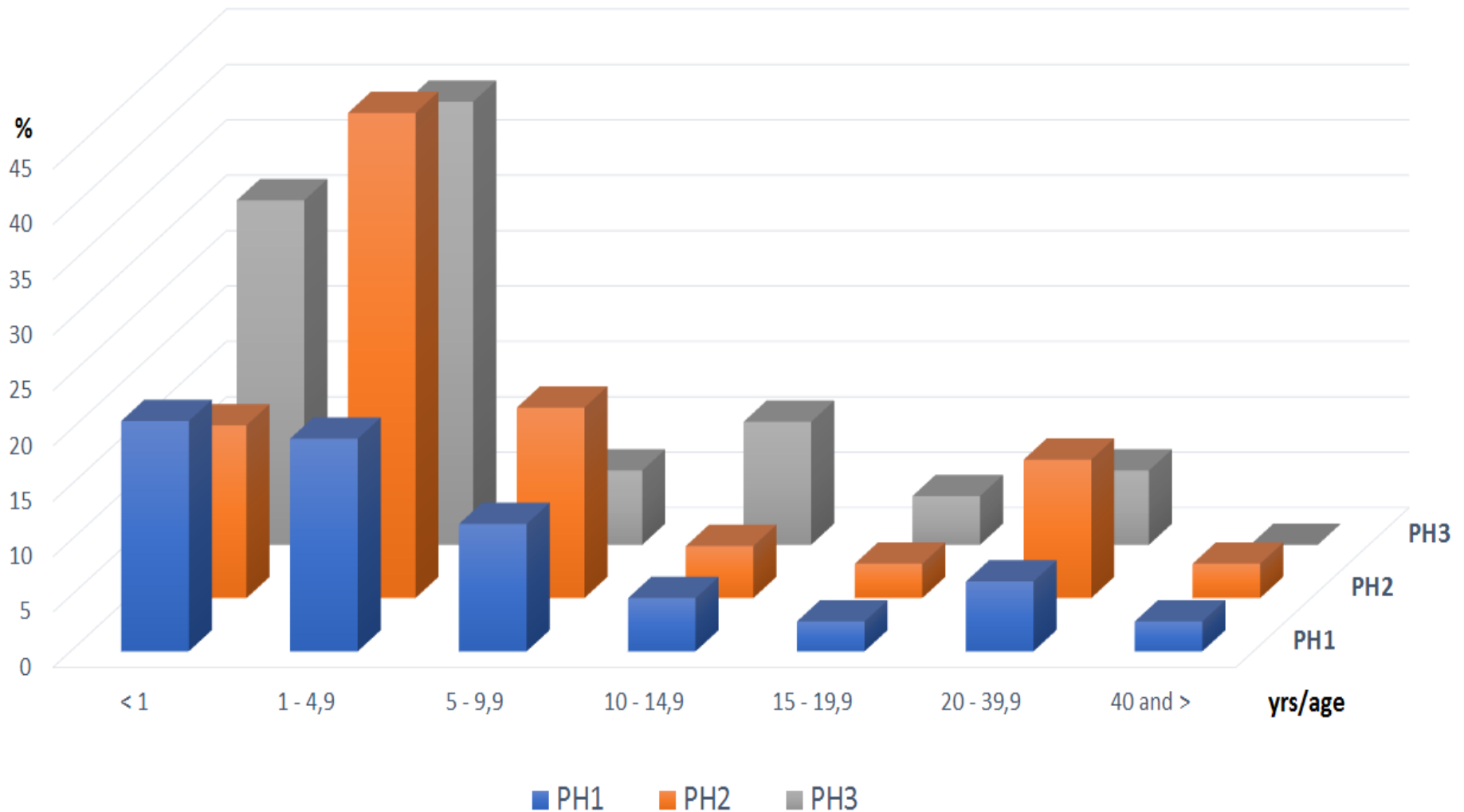
- **PH1** **AGXT gene *chr 2***
→ plasma oxalate + glycollate
→ urine oxalate
- **PH2** **GRHPR gene *chr 9***
→ urine L-glyceric acid (may be absent)
- **PH3** **HOGA1 gene *chr10***
→ urine oxalate + glycollate
→ urine Ca + uric acid

Database of pathological mutations + polymorphic variants
<http://www.uclh.nhs.uk/phmd>

Urine oxalate excretion in PH1, PH2 and PH3 illustrating overlap of urine oxalate/creatinine ratio



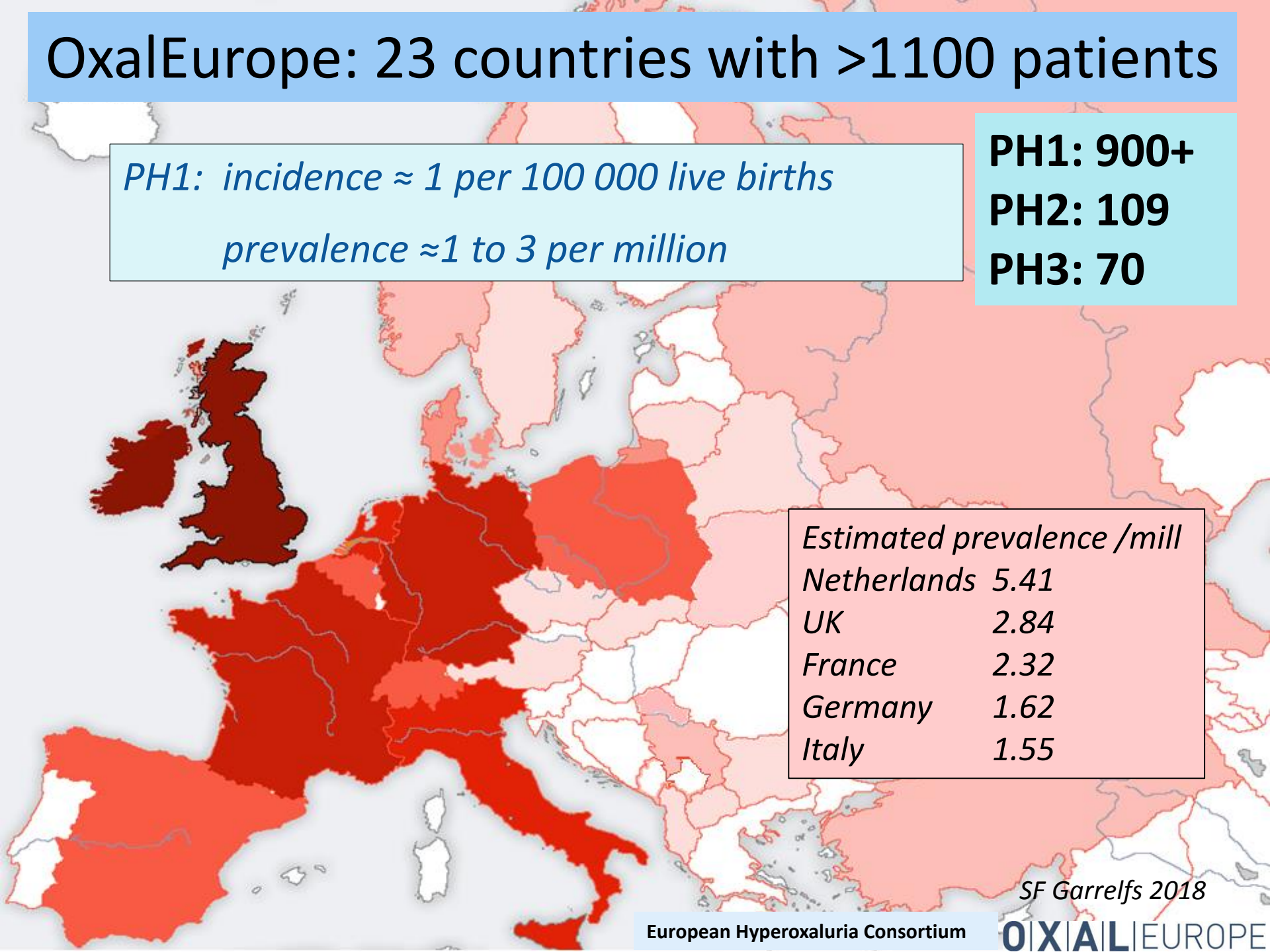
Age of onset: PH1, 2 and 3



OxalEurope: 23 countries with >1100 patients

PH1: incidence $\approx$ 1 per 100 000 live births
prevalence $\approx$ 1 to 3 per million

PH1: 900+
PH2: 109
PH3: 70



Estimated prevalence /mill	
Netherlands	5.41
UK	2.84
France	2.32
Germany	1.62
Italy	1.55

SF Garrelfs 2018

PH under diagnosed in Middle East and Asia



- ↑ U oxalate 24- 40% of Pakistani children with stones¹. 150 PH1 Pakistani patients studied²
- Estimates of high disease burden: incidence of 1 in 14 500 (based on UK data³) with gene frequency ranges from 1 in 4000 to 200 000⁴ (cf 1 in 200 000 in Europeans)
- Incidence:
Pakistan: 1 in 1000 - 50 000
Morocco: 1 in 27 500 - 32 000
- Diagnosis often missed or delayed⁴
 - Lack of availability of adequate diagnostic tools
 - Highly variable age of onset, presentation and progression

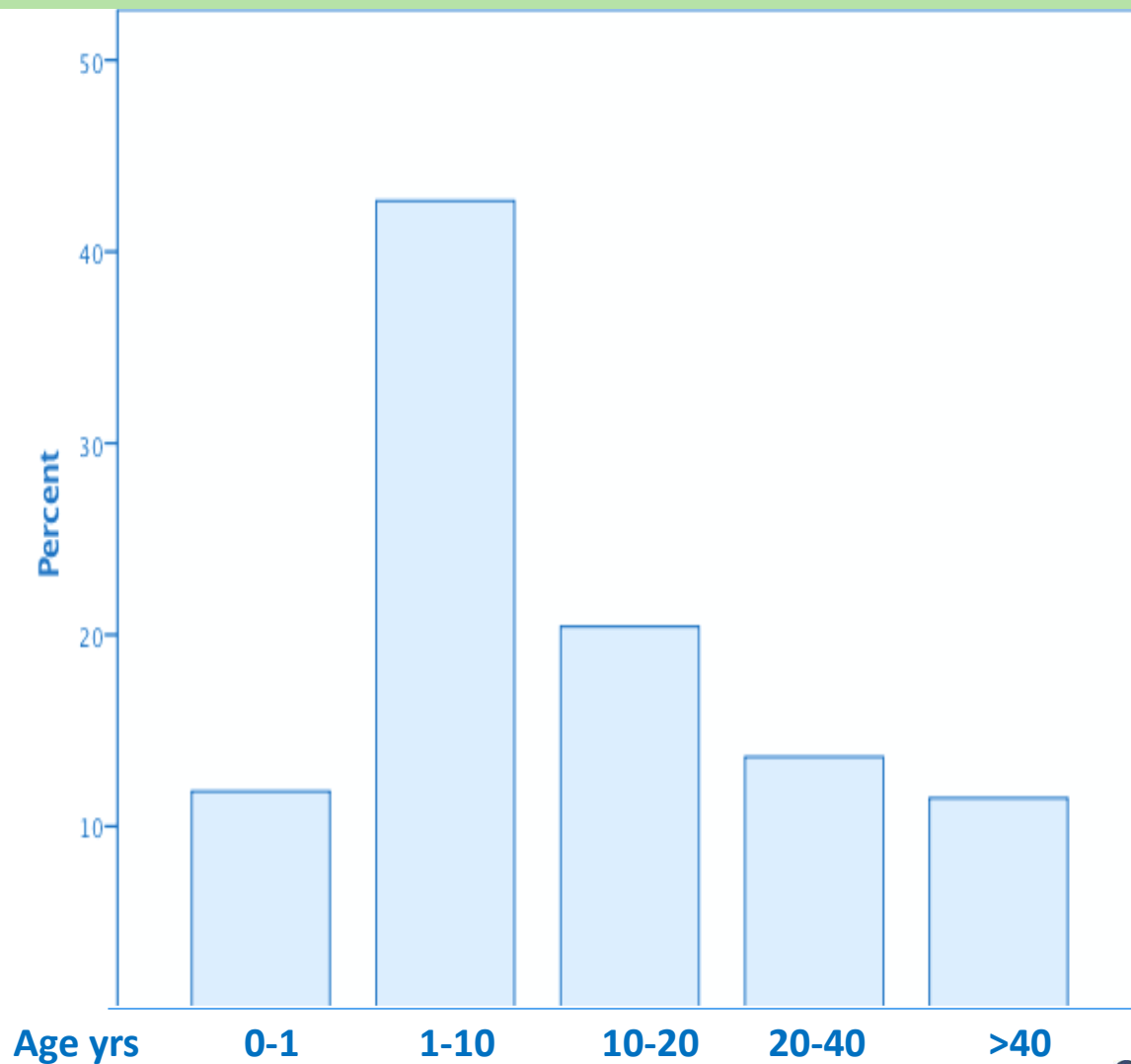
¹Rizvi SA et al. *Ind J Urol* 2007; 23(4) 420-7

²Khaliq S et al. *Abstract: Am Soc Hum Gen* 2013

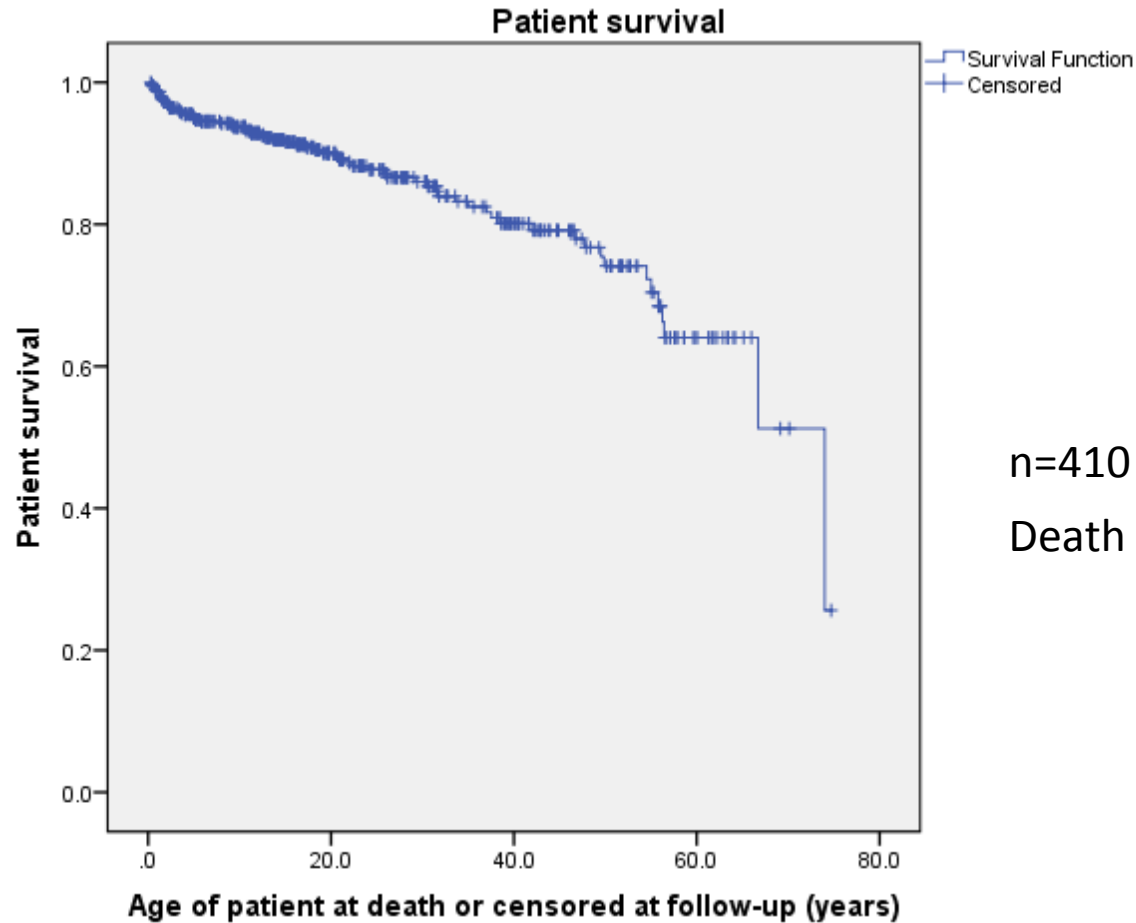
³Hutchesson AC et al. *J Med Gen* 1998;35(5) 366-70

⁴Talati JJ, Hulton SA et al. *Urolith* 2018;46 (2) 187-95

PH1: age at diagnosis n=297



PH1 patient Kaplan-Meier survival curve



n=410 with full AGXT genotype
Death in 13%

Renal failure in childhood PH1

- Consanguineous families – high prevalence
- <1% of paediatric ESRD in USA, UK¹, Japan²
- 10 % for Kuwait³
- 13% for Tunisia⁴

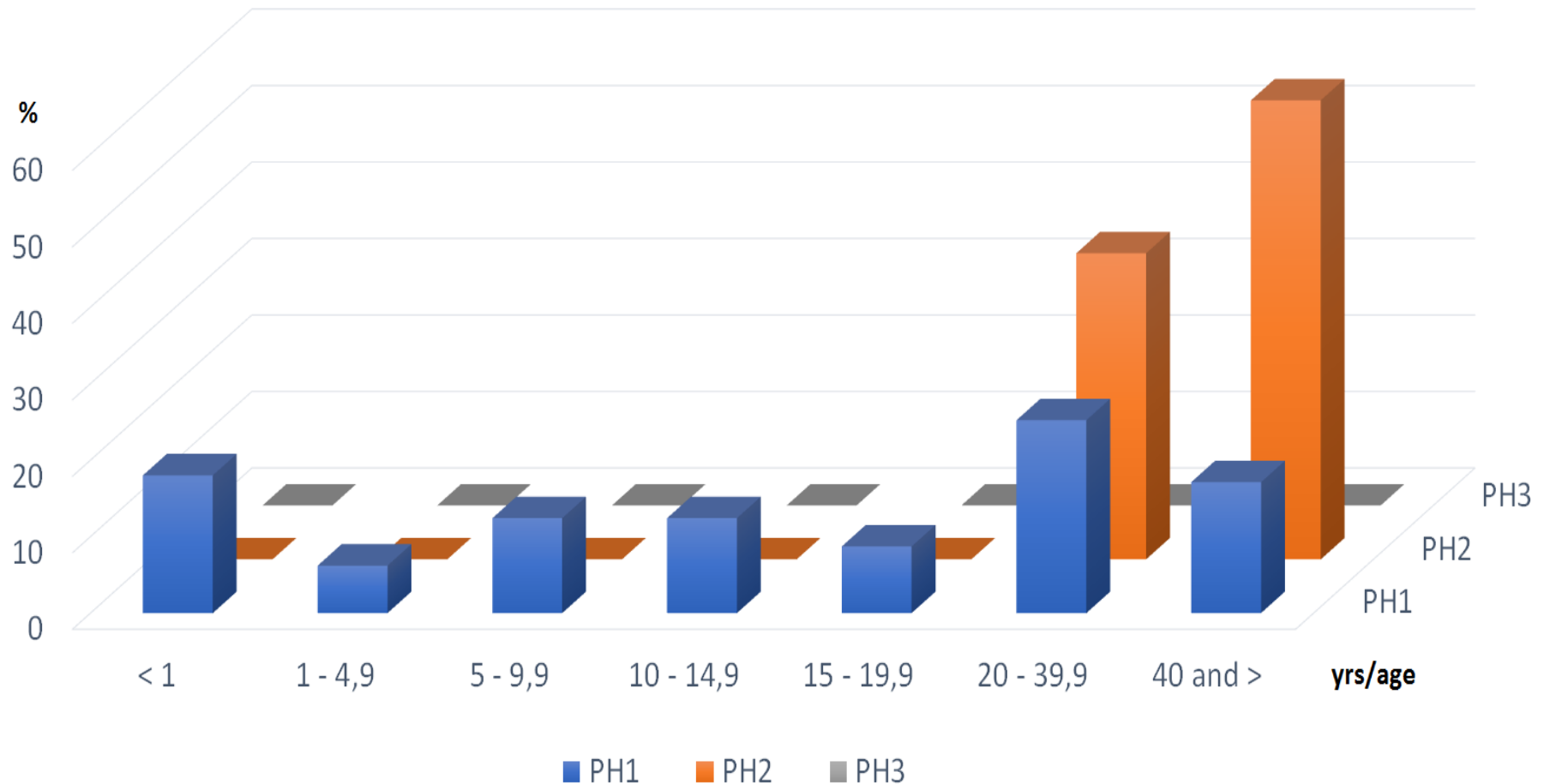
¹ NAPRTCS and UK Renal Registry Annual Reports

² *Ped Nephrol* 2002, 17 (6) 456–61

³ *Transpl Proc* 2004, 36 (6) 1788–91

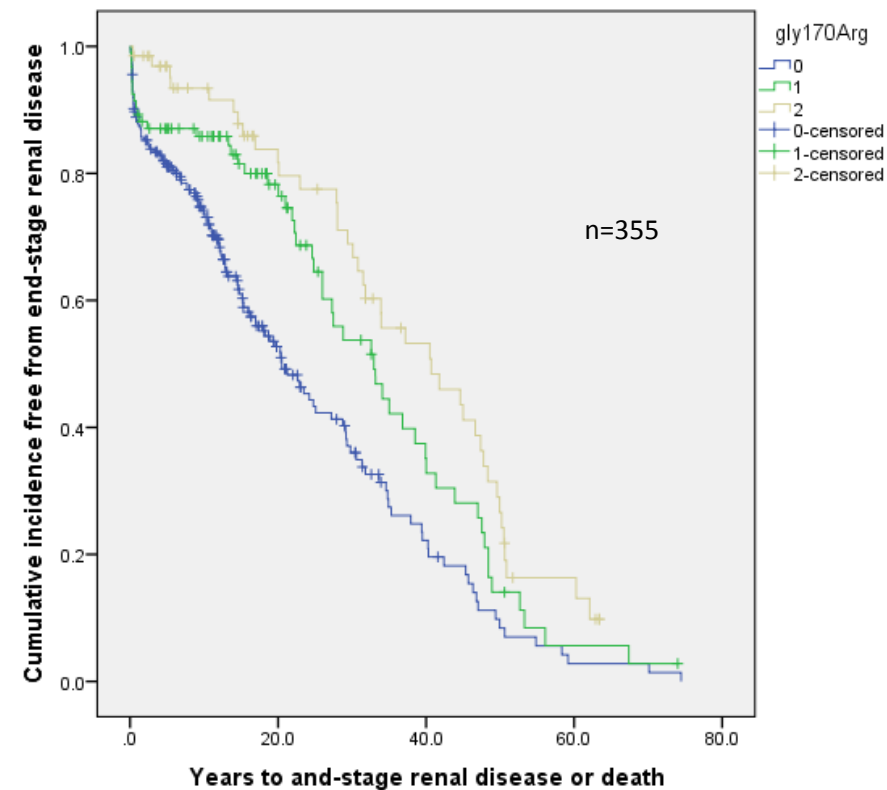
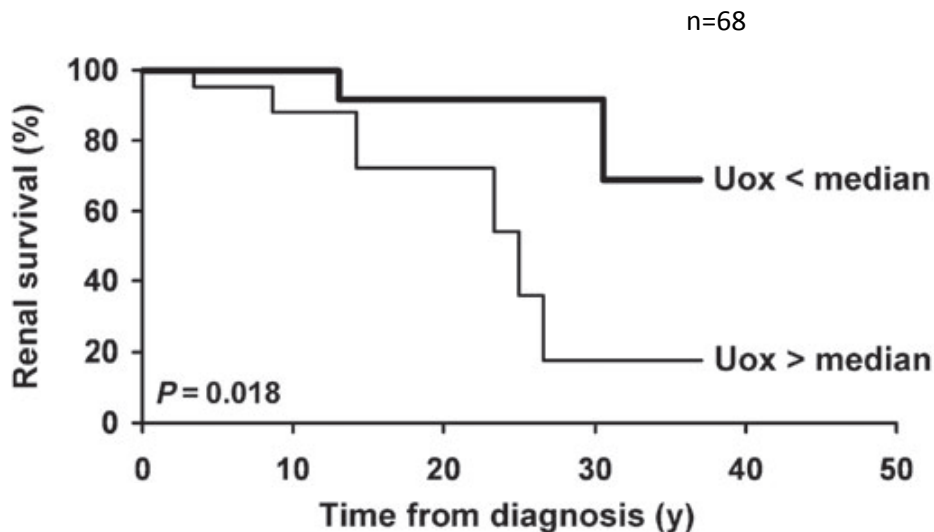
⁴ *Ped Nephrol* 1996, 10, (4) 479–82

Age at time of kidney failure ESRD – PH1 vs PH2

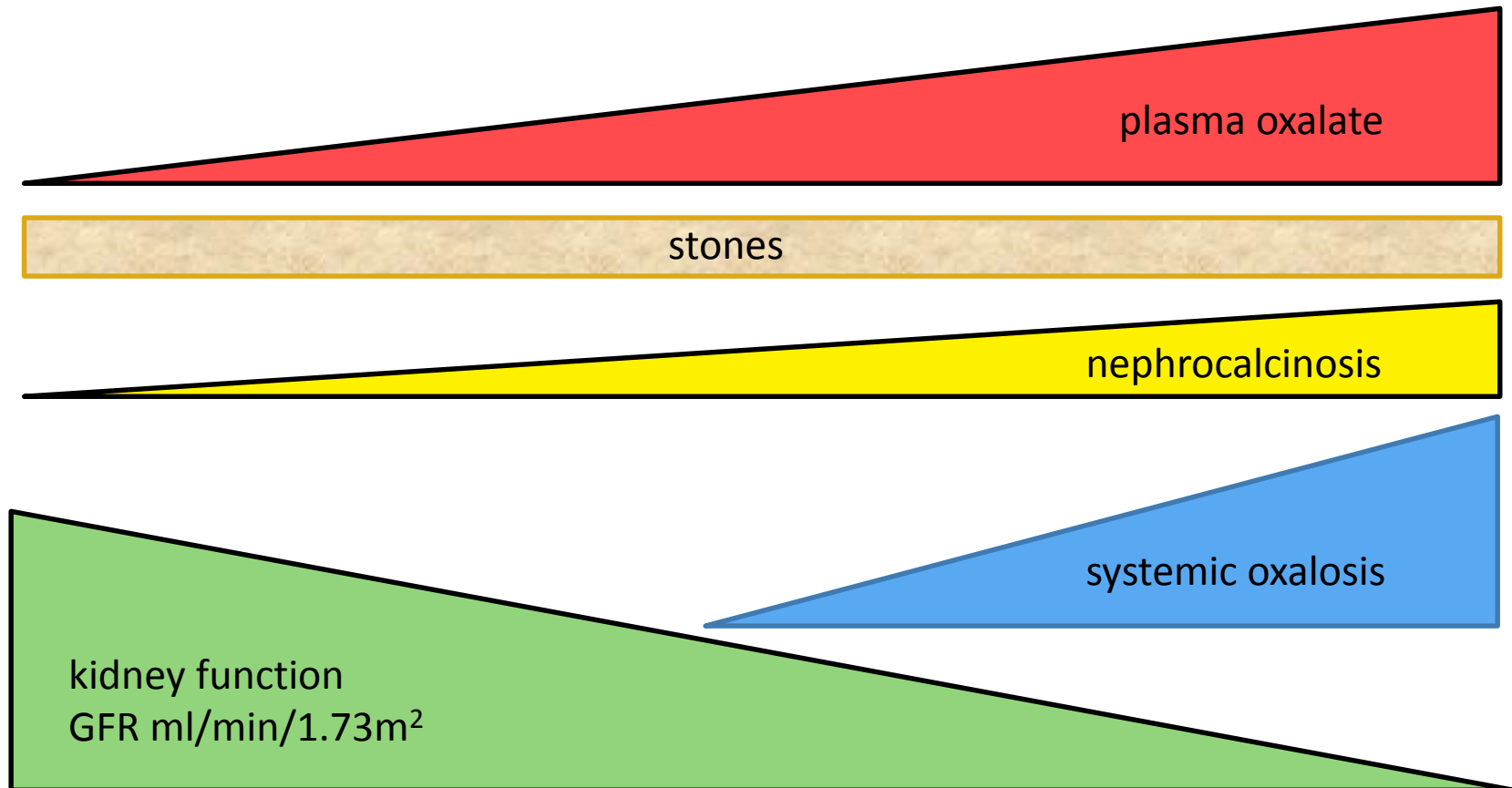


Factors impacting on renal survival

- Degree of hyperoxaluria
- Specific mutation
- Nephrocalcinosis



Progression of systemic oxalosis



CKD stage 1 > 90	CKD stage 2 60 - 89	CKD stage 3 30 -59	CKD stage 4 15-29	CKD stage 5 <15
Normal, ↑ Uox, PH genes	Mild impairment	Moderate impairment	Progressive decline	End stage renal disease

Consequences of PH1

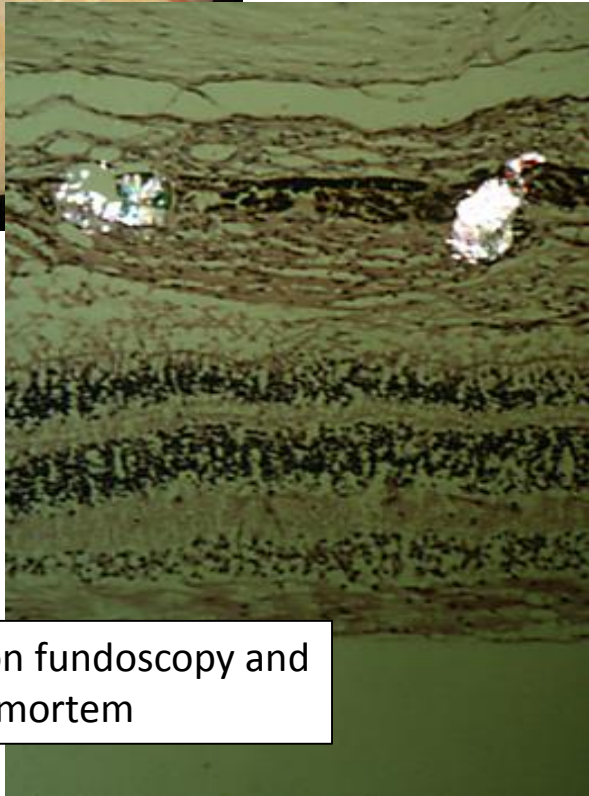
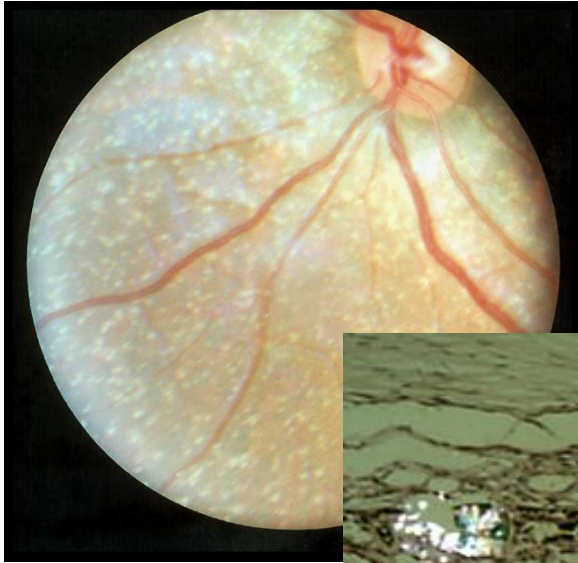
- Phenotypic variability
- Progressive renal impairment
- Systemic deposition of Ox in all organs
 - bones
 - myocardium, vasculature, AV block
 - cutaneous
 - bone marrow: EPO resistant anaemia
 - eyes: retina
 - neurological

51 of 132 PH1
patients →
systemic
oxalosis¹

¹Garrelfs S et al. On behalf of
OxalEurope; IPNA 2016

Consequences of PH1

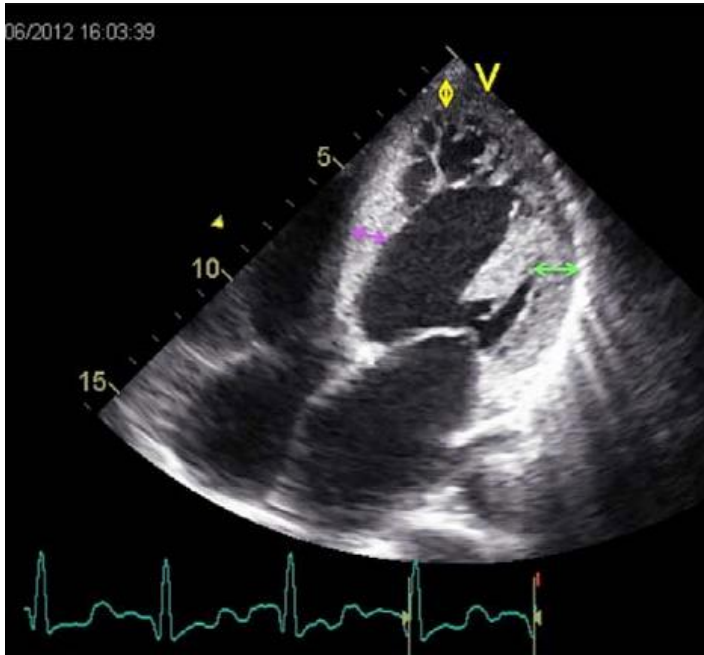
Female aged 9 years with calcification of kidneys, marked osteopenia. Pin in femoral neck following fracture.



Oxalate crystals on fundoscopy and in retina on post mortem



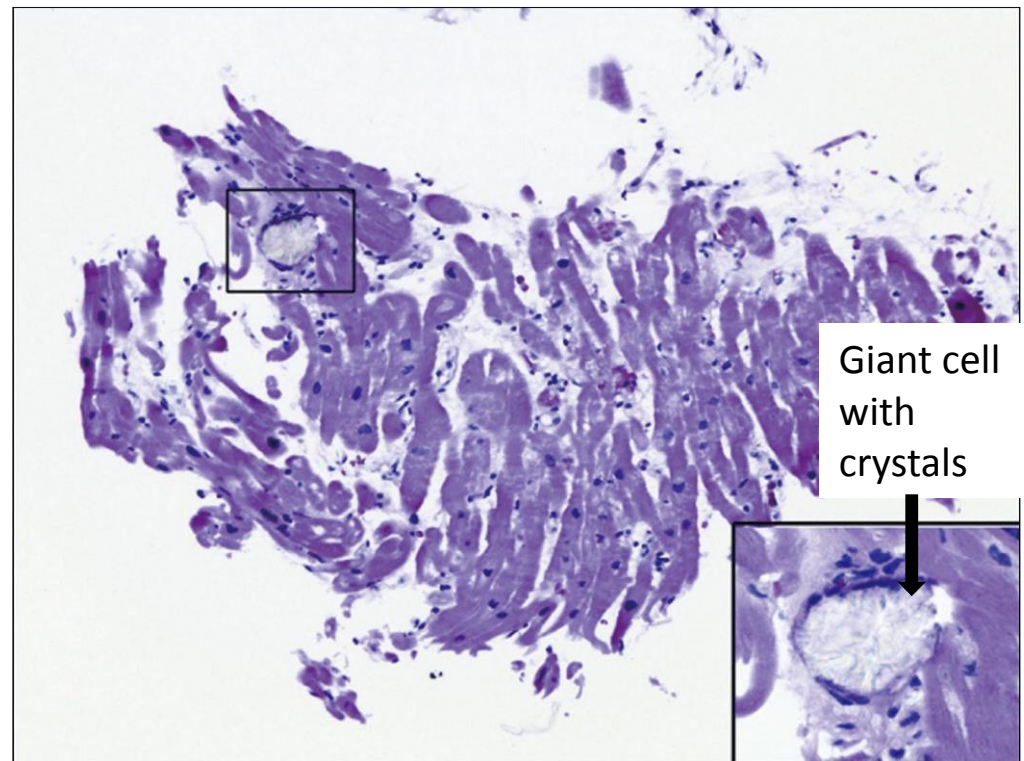
Consequences of PH1



Cardiac echo showing increased wall thickness

CR Lagies et al: Circ Heart Fail 2013;6: e45-7

Endomyocardial biopsy right ventricle



F Mookadam et al: Circ J 2010; 74: 2403 – 2409

Consequences of PH1



Livedo reticularis of skin



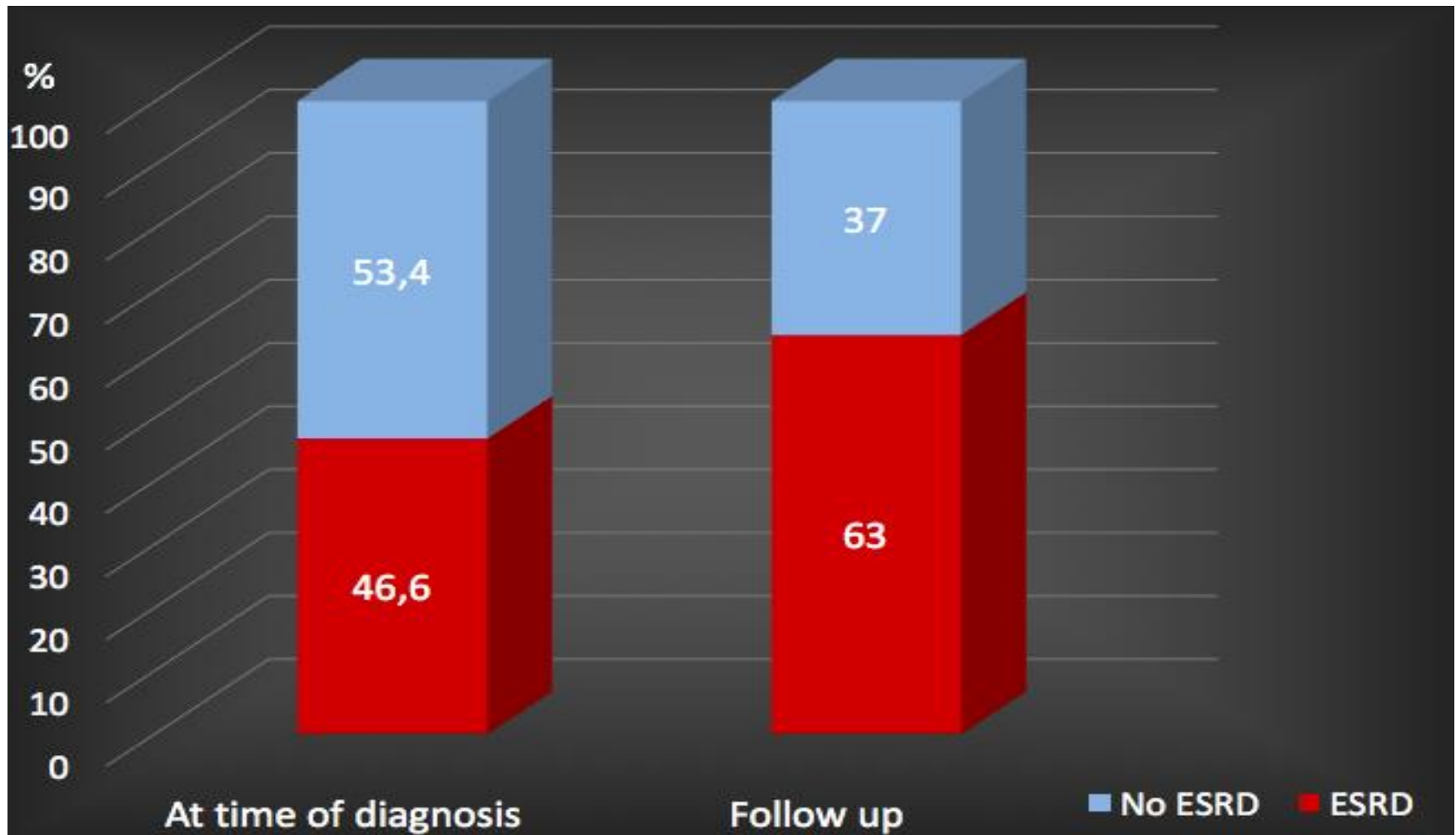
Index and middle finger

Gangrene of fingers with osteolysis in secondary oxalosis



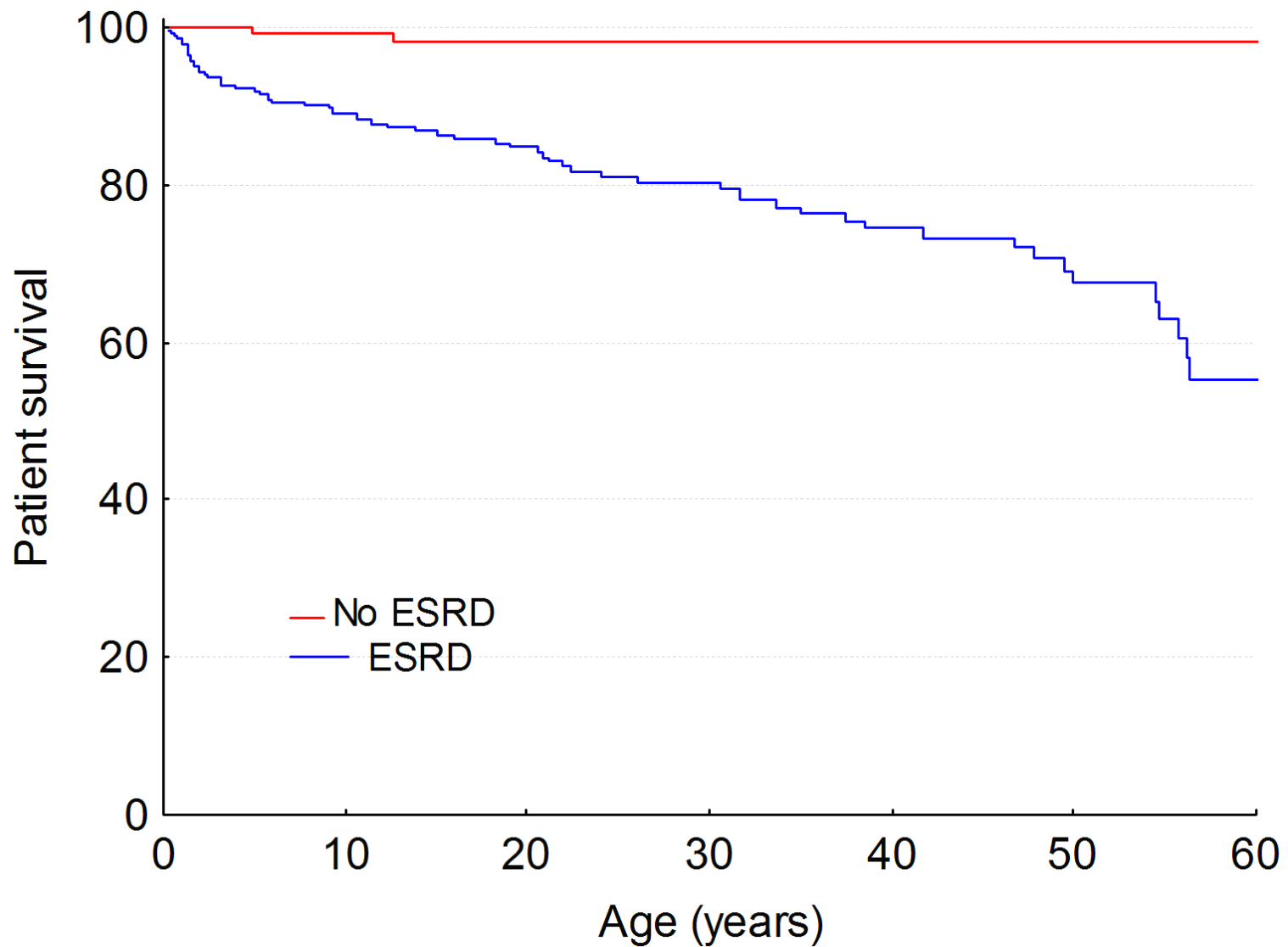
Courtesy of S Arampatzis, D Fuster
University Hospital of Bern, Switzerland

Renal Impairment – PH1



ESRD at time of diagnosis
< 18 years (34 %)
> 18 years (74 %)

Patient survival PH1: importance of ESRD



Infantile Systemic Oxalosis

- Poorer prognosis for PH1 in neonates
- Early death is common
 - 50% have ESRD at diagnosis and 80% develop ESRD by 3 years¹
- Difficult to diagnose and treat
 - Normal ranges of urinary/plasma oxalate not clearly defined for neonates
 - Acute renal failure common problem in infancy: hampers urinary excretion of oxalate
- Only effective treatment option early hepato-renal transplantation

¹ Millan et al. *Transplantation*. 2003; 76:1458-63

Early diagnosis + therapy

- affects long term outcome
- 20/27 PH1 children stable GFR over 20yrs
- document genetic data
- allows time to reflect on phenotypic variability

Fargue S et al KI 2009; 76: 767-73

Conservative treatment

1. Minimize absorption of oxalate
 - Avoid Vit C / high oxalate foods
 - *Oxalobacter formigines*
2. Reduce oxalate synthesis
 - Vit B6 pyridoxine
 - Gly170Arg or Phe152Ile mutation
3. Minimize oxalate deposition in kidney
 - ↑ Fluid intake 2.5 l/m²/day minimum
 - ↓ Salt Na⁺ intake
 - Potassium citrate to reduce urine acidity

On-going management

Annual GFR ml/min/1.73m²

- If > 60 → stable
- If 40-60 → consider isolated liver Tx
review genotype *Gly170Arg*
- If < 40 → combined liver/ kidney Tx

Dialysis in PH

- Unable to reduce oxalate load
- Weekly clearance = 6-9 mmol/wk/SA
equivalent to 2 days of endogenous oxalate production
- Haemo clearance better at 120ml/min than PD at 7ml/min

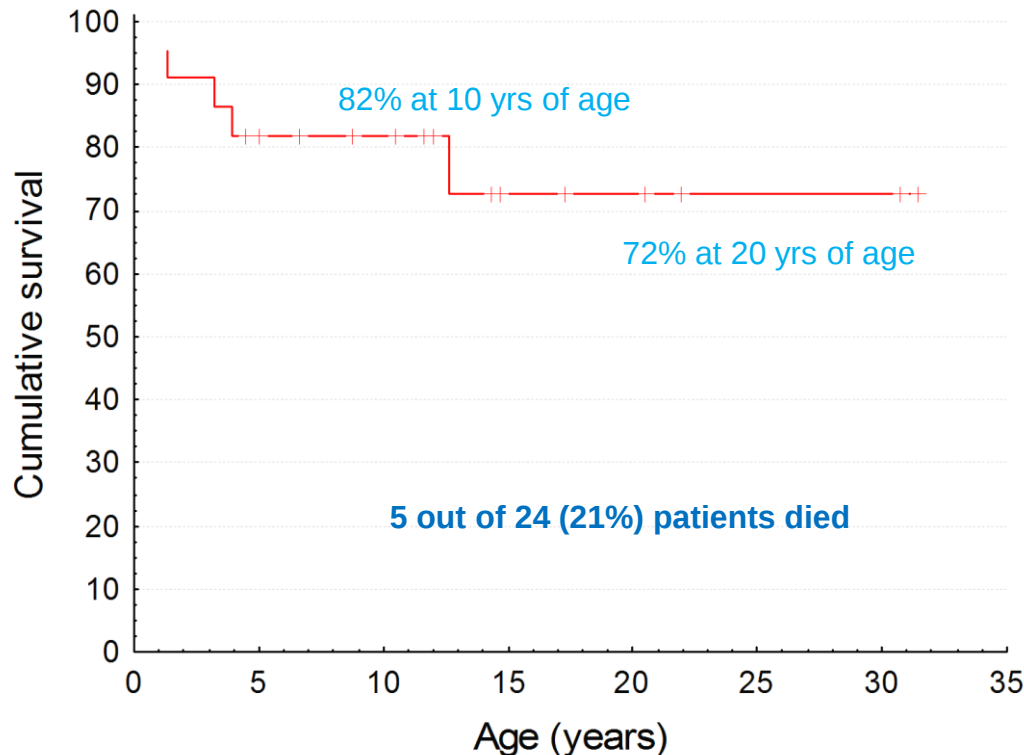


Am J Kid D 1992; 19: 546-53
Perit Dial Int 1994; 14: 81-84
NDT 2001; 16: 2407-11
KI 2006; 70: 1642-8

Isolated liver transplant

- ? Timing + genotype *Gly170Arg*
- Drugs compromise renal function
- Possible subsequent renal Tx

**Patient
survival in
pre-emptive
Liver Tx**



Perera T et al NDT 2010; 26(1)354-9
Ped Transpl 2000; 4: 177-81

Hepato-renal transplantation

- Combined

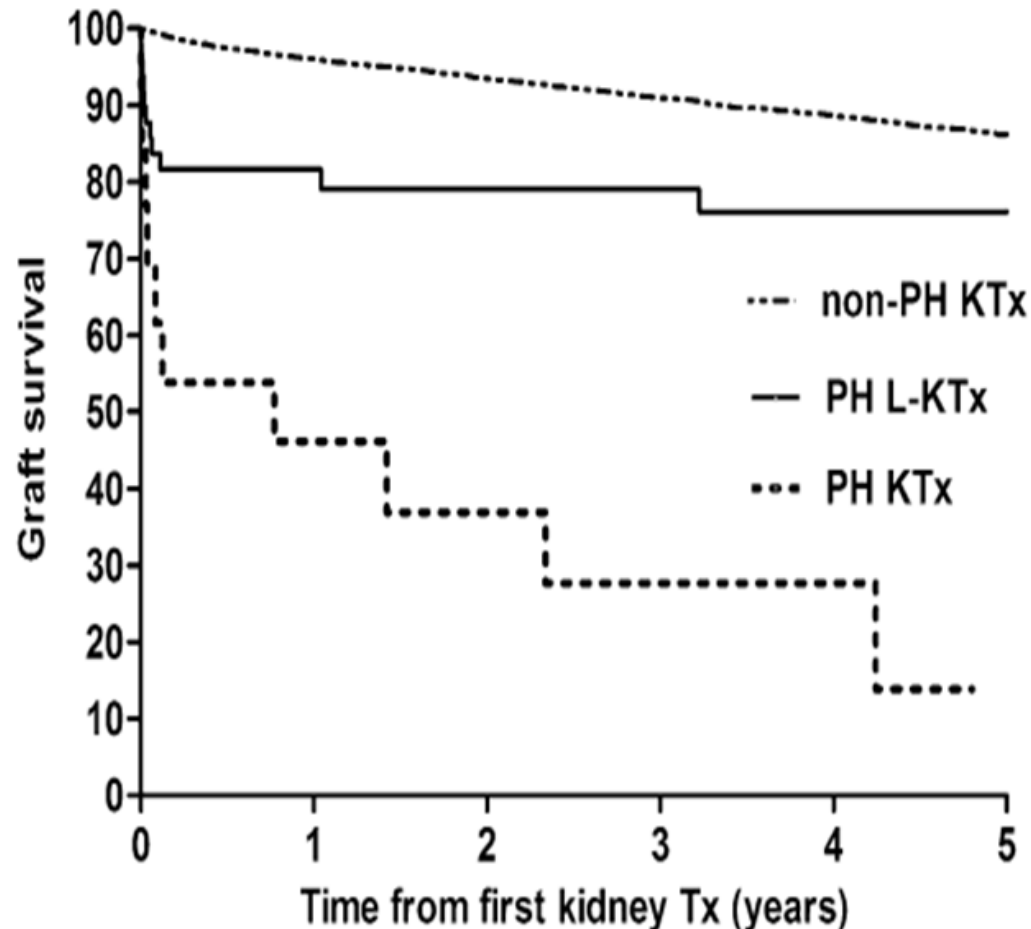
- Total hepatectomy required
- 80% patient 5yr survival with GFR of 40-60
- Risk factors:
 - age < 5 yrs
 - dialysis > 2 yrs
 - poor renal graft function

- Sequential

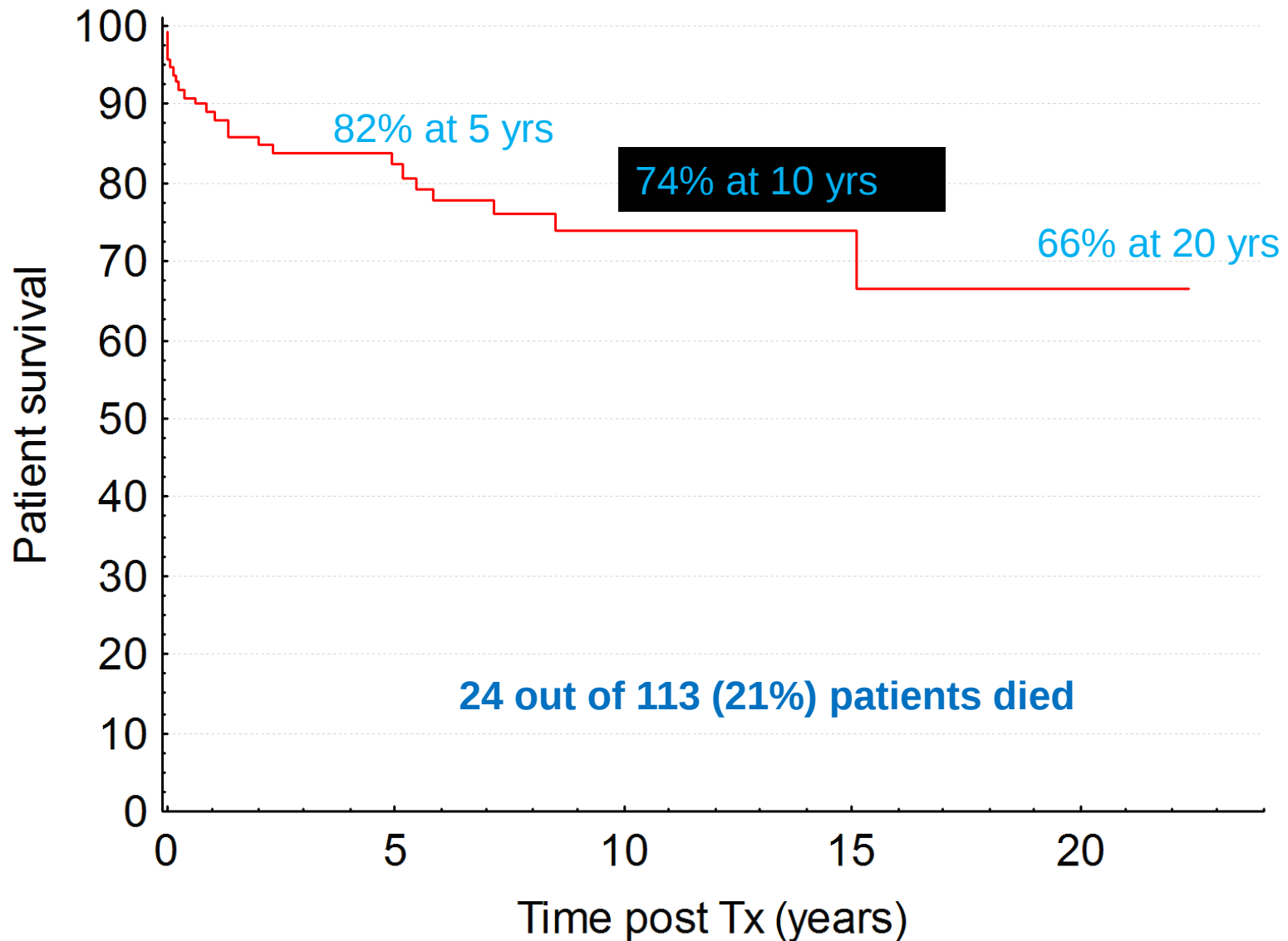
- liver 1st then kidney
 - advantage of early liver replacement of AGT
 - can delay renal Tx
- cadaveric or LRD or combination

Transplantation approach in PH1

5-year kidney graft survival



Patient survival after combined hepato-renal transplant



Current problems

- Increasing awareness of PH to provide equity of care
- Management of recurrent stones
- Prediction / prevention of decline in renal function
- Oxalate deposition systemically and in the transplanted kidney – sometimes immediate graft loss

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Oxalosis & Hyperoxaluria Foundation

STEPPING STONES TO A CURE

WELCOME TO THE OHF

The Only Foundation In The World
Dedicated to improving the care and treatment
and finding a cure for Oxalosis, Primary
Hyperoxaluria and other hyperoxaluria related
stone diseases.



SINCE 1989...

The OHF has been uncovering the secrets of Primary Hyperoxaluria, investing millions of dollars in research to find better treatments and cure.



Donate



Learn



Research



Advocate



People





NORD[®]
National Organization for Rare Disorders

RareDiseaseFacts™

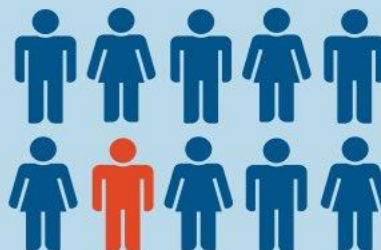


What is a **RARE DISEASE** ?

Any disease, disorder, illness or condition affecting **fewer than 200,000** people in the United States is considered RARE.¹

1 in 10

Americans has
a **RARE DISEASE**
30 million people
have a serious,
lifelong condition.



Holding hands,
they would circle
the globe about
1.5 times

More than half are children¹



7,000

RARE DISEASES
exist, with less than 500
FDA-approved treatments²

ONLY 5% of **RARE DISEASES** have treatments.²

Patients with RARE DISEASES are frequently **misdiagnosed or undiagnosed**.



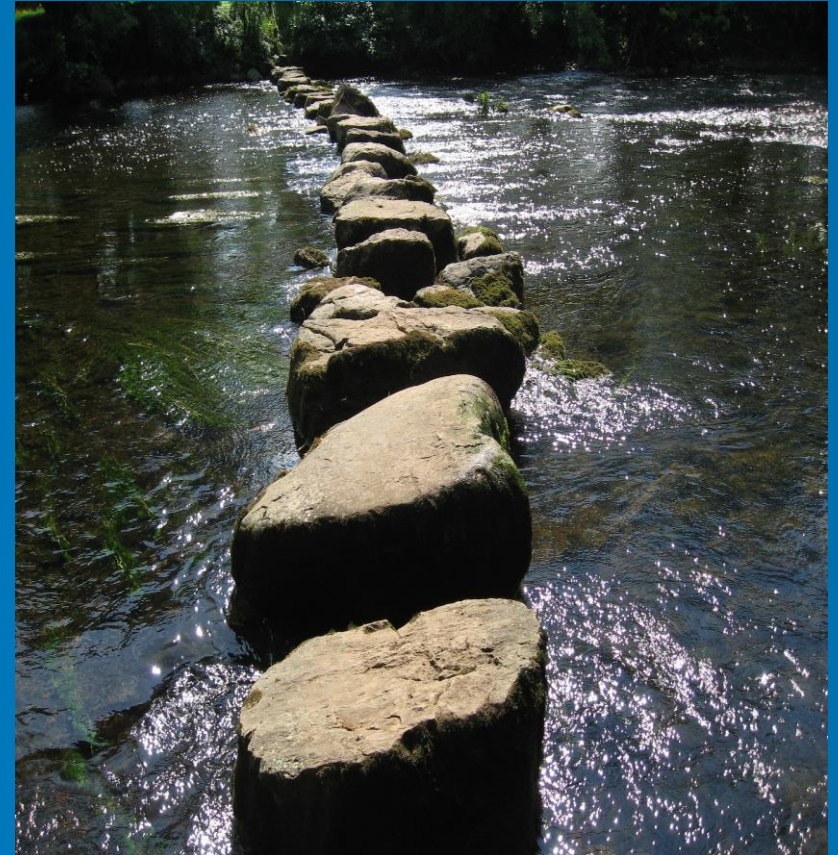


Oxalosis & Hyperoxaluria Foundation

STEPPING STONES TO A CURE



To learn more, visit: Ohf.org



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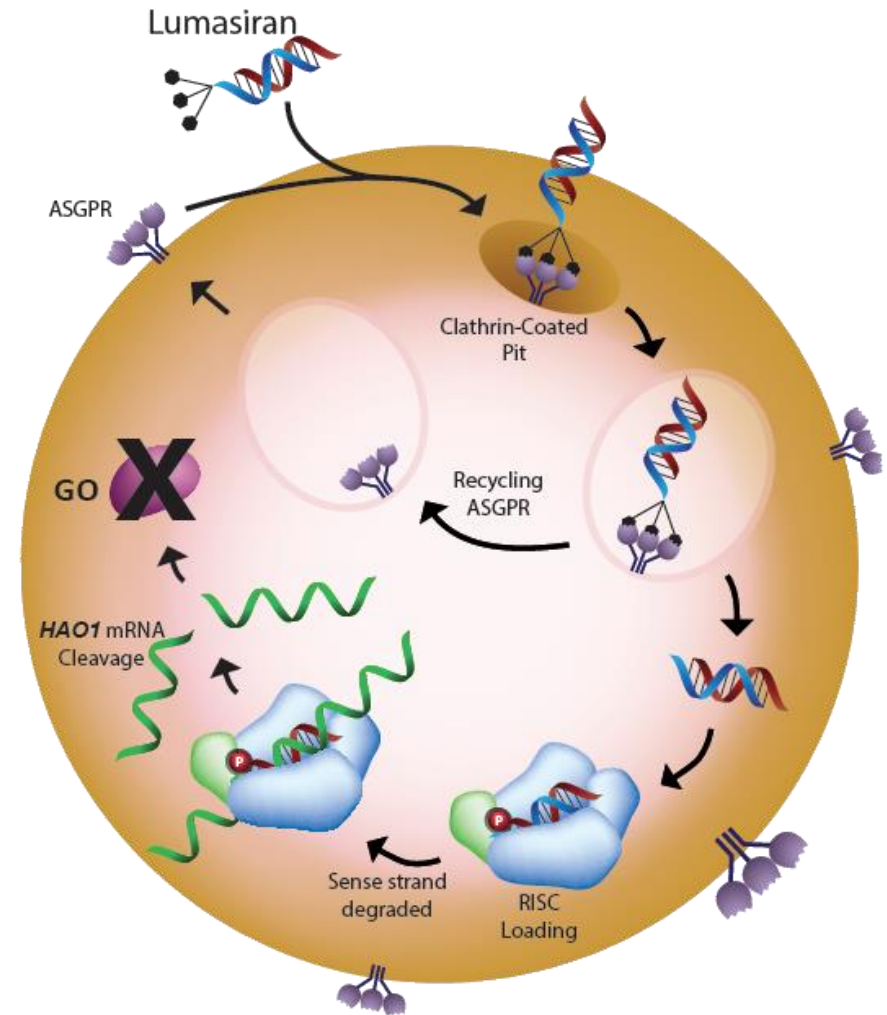
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- Pritesh Gandhi, PharmD., Vice President, General Manager, Lumasiran

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Lumasiran (ALN-GO1)

Lumasiran is an investigational RNAi therapeutic targeting glycolate oxidase (GO) in development for treatment of Primary Hyperoxaluria Type 1 (PH1)

Lumasiran is designed to reduce hepatic levels of GO enzyme (encoded by *HAO1*), thereby depleting substrate necessary for oxalate production, which directly contributes to pathophysiology of PH1

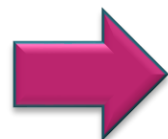


Lumasiran Therapeutic Hypothesis

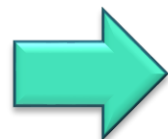
Knockdown of Liver GO Enzyme to Reduce Oxalate



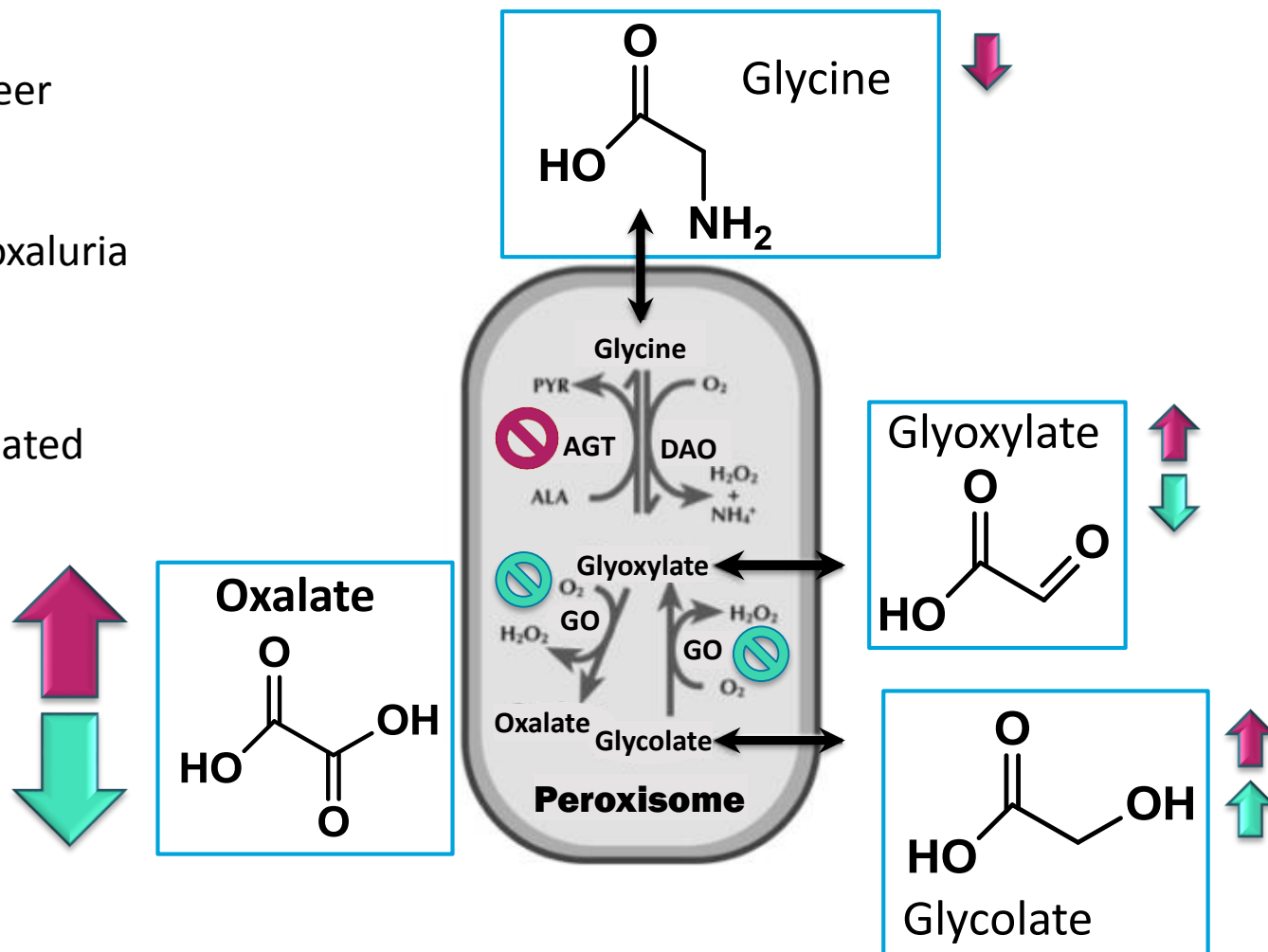
Healthy Volunteer



Primary Hyperoxaluria
Type 1 Patient

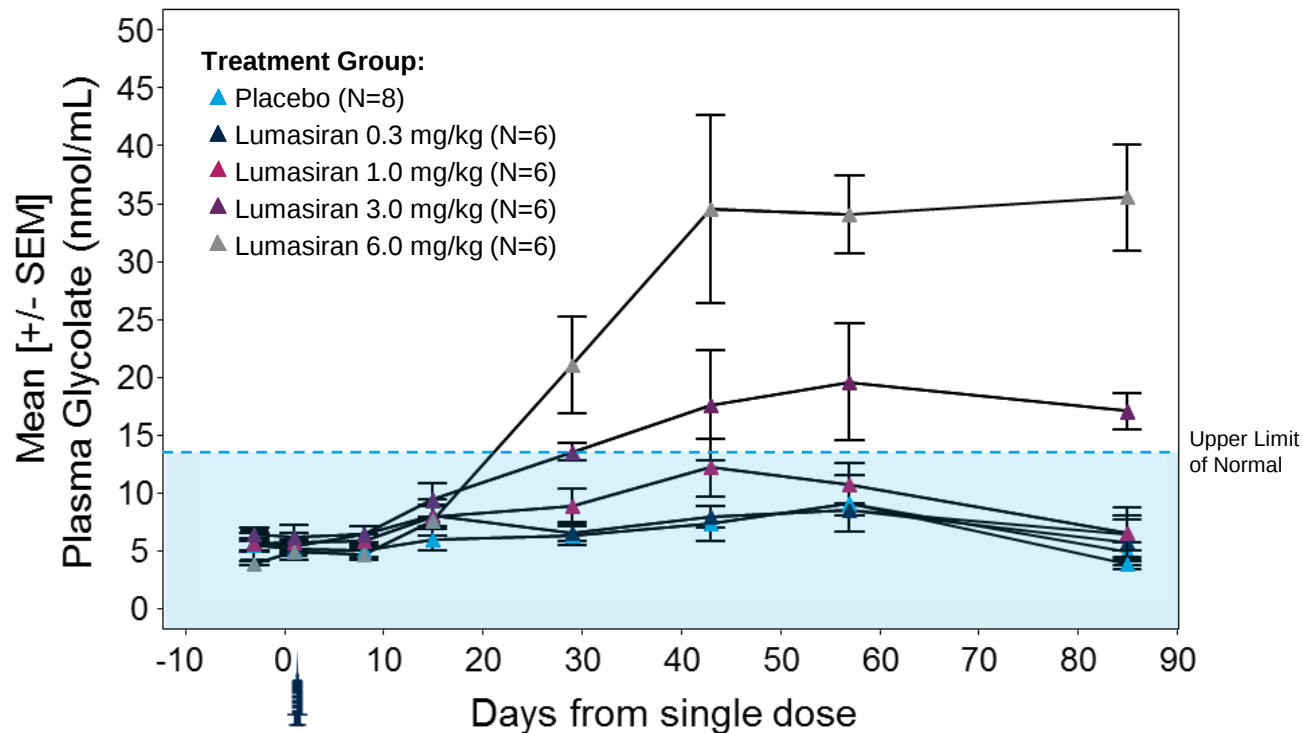


PH1 Patient Treated
with Lumasiran



Lumasiran Phase 1/2 Part A Study Results: Plasma Glycolate Levels in Healthy Volunteers

Dose-dependent increase in plasma glycolate levels in healthy volunteers after single dose of lumasiran¹



- No reports of Serious Adverse Events
- Majority of AEs were mild or moderate; one severe AE, not related to study drug
- Most common treatment related AE reported was self-limited localized pain at injection site during drug administration (4 patients, 17%)

Reported Cases of Known or Suspected GO Inactivity

Lumasiran targets GO, key enzyme in pathway of hepatic oxalate production. Many patients with PH1 already have elevated glycolate levels as part of their disease pathophysiology. No known negative impact of elevated glycolate levels.

8 year old boy¹ • Marked elevations of urinary glycolate • Homozygous deleterious <i>HAO1</i> mutation • Healthy liver and healthy kidneys • Triple A-like Syndrome (<i>GMPPA</i>)	14 month old boy² • Marked elevations of urinary glycolate • Normal AGT activity on liver biopsy • Healthy liver and healthy kidneys • <i>HAO1</i> not sequenced
Adult woman³ • Homozygous <i>HAO1</i> mutation detected as part of broad sequencing effort • Healthy liver and kidneys • Three healthy pregnancies	9 month infant girl⁴ • Congenital Hyperinsulinism (<i>ABCC8</i>) • Marked elevations of urinary glycolate • <i>HAO1</i> mutations detected • Elevated oxalate in spot urines • Negative sequencing for PH1/PH2/PH3

AGT, alanine:glyoxylate aminotransferase; GO, glycolate oxidase; PH, primary hyperoxaluria

1. Frishberg Y, et al. *Journal of Medical Genetics*. 2014; 2. Craigen WJ. *J Inherit Metab Dis*. 1996;

3. Narasimhan VM, et al. *Science*. 2016; 4. Clifford-Mobley O, et al. *Pediatr 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



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/1.73m²
- Urinary oxalate excretion ≥ 0.70 mmol/24h/1.73m²



Dosing Complete

Lumasiran Phase 1/2 Study*

Patient Demographics & Exposure: Part B (Patients with PH1)

Characteristic	Result (N=20)
Mean age, years (range)	14.9 (6–43)
Age <18 years	80 %
Gender, females	65 %
Mean weight, kg (range)	49.9 (21.3-110.0)
Mean eGFR, mL/min/1.73m ² (range)	77 (42–131)

Lumasiran Phase 1/2 Study Initial Results*

Safety: Part B (Patients with PH1)

Multiple doses of lumasiran well tolerated in patients with PH1

75% of patients (n=15) with PH1 reported at least one adverse event (AE)

- No AEs led to study discontinuation
- Most AEs were mild or moderate in severity and unrelated to study drug
- 2 patients reported severe AEs; 1 patient with pyelonephritis during placebo dosing; 1 patient with renal colic and kidney stone after lumasiran dosing deemed unrelated to study drug
- Most common AEs (≥ 3 pts) were abdominal pain, headache, nasopharyngitis, pyrexia, and vomiting; all unrelated to study drug
- Injection site reactions have been reported in 2 patients; ISRs have been mild, transient and self-limited

Serious Adverse Events (SAEs)

- One patient had SAEs of nephrolithiasis and pyelonephritis during placebo dosing
- Three patients had SAEs after lumasiran dosing; one patient with nephrolithiasis, one patient with gastroenteritis, and one patient with abdominal pain and pyrexia
- No SAEs were considered related to study drug

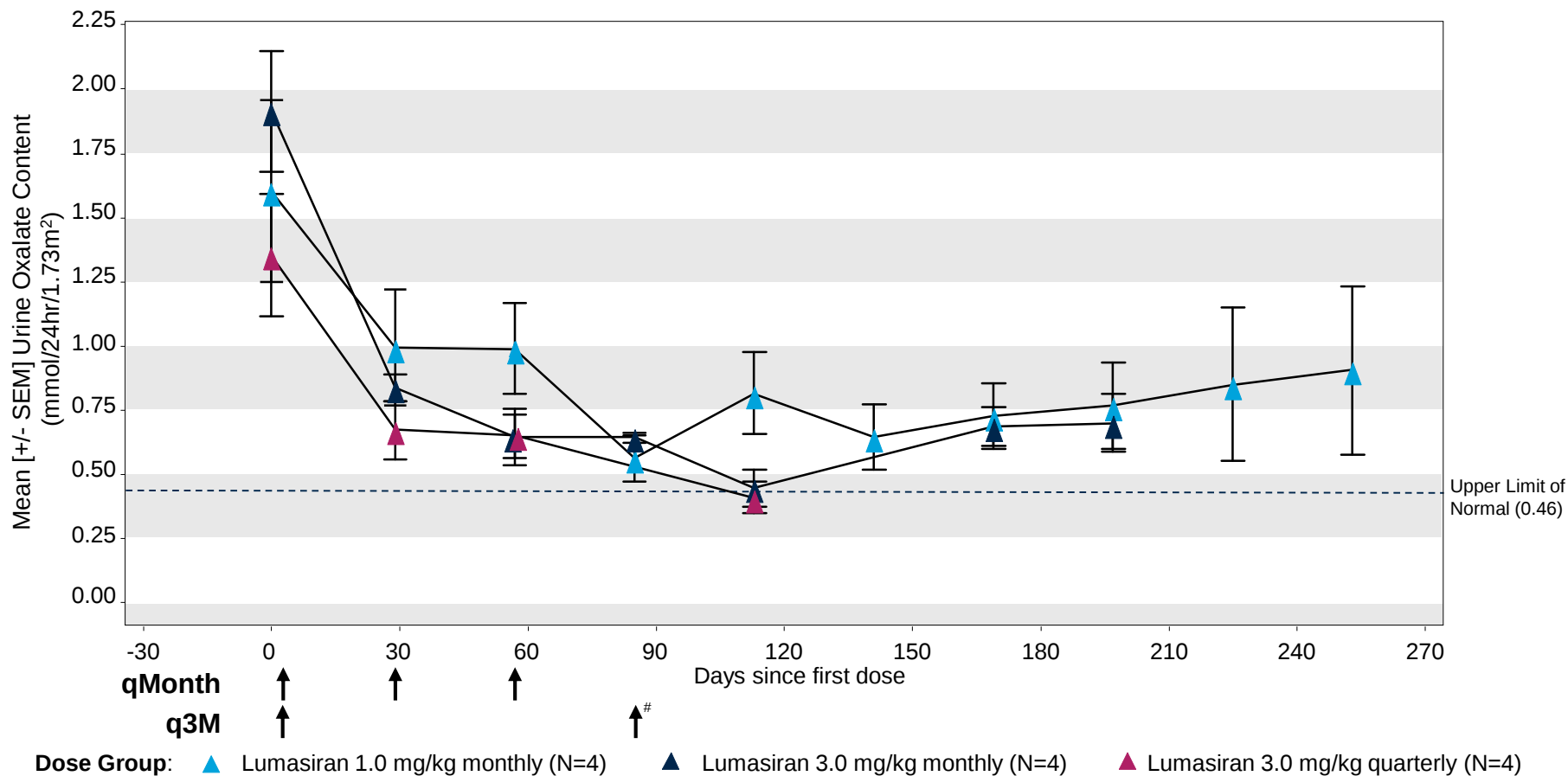
No clinically significant laboratory or hematologic changes

Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Part B (Patients with PH1)

Mean maximal reduction in urinary oxalate of 64% relative to baseline after lumasiran dosing in patients in Cohorts 1-3 (n=12)

- Mean 63% urinary oxalate reduction relative to baseline observed at day 85 (n=9†)



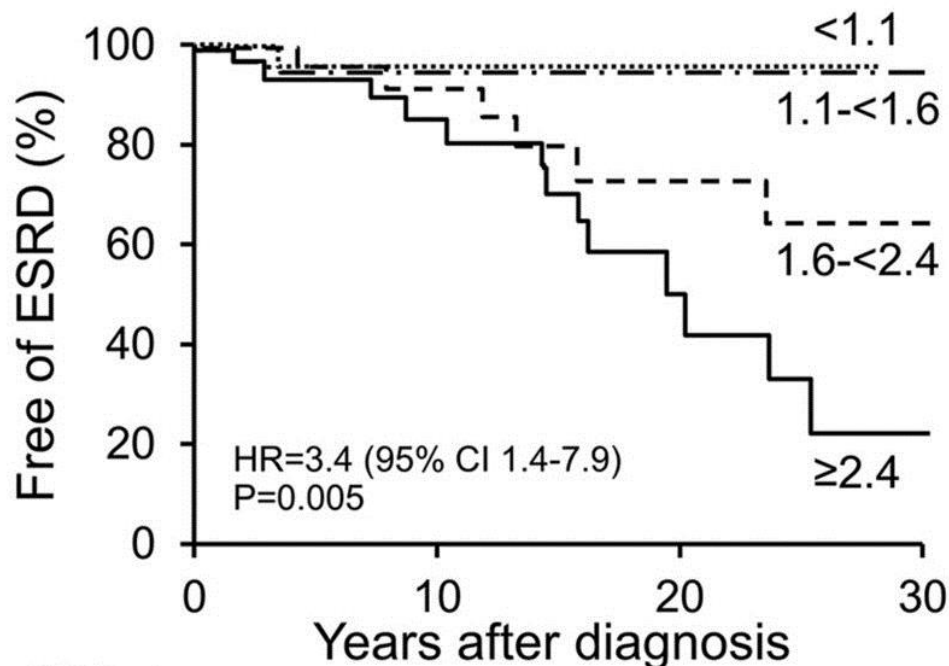
*Data as of: March 29, 2018; Only data points with at least 3 contributing patients are represented.

†Patients who completed the Study Day 85 visit and had a valid 24-hour urinary oxalate assessment

Placebo patient in quarterly cohort had not yet reached Day 85 post lumasiran dosing

Significance of Decreasing Urinary Oxalate

Lumasiran lowered UOx below 1.1 mmol/24hr/1.73m² in all patients with baseline excretion ≥ 1.6 mmol/24hr/1.73m²



Renal survival was examined by quartile of urine oxalate (UOx) excretion (mmol/24hr/1.73m²) at diagnosis of patients enrolled in the RKSC PH registry. 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.

Lumasiran Phase 1/2 Initial Study Results*

Summary and Next Steps

Lumasiran (ALN-GO1) is a subcutaneously administered investigational RNAi therapeutic designed to reduce hepatic production of oxalate in patients with Primary Hyperoxaluria Type 1 (PH1)

Multiple doses of lumasiran have been well tolerated by patients with PH1 with no drug related SAEs or discontinuations from study

Patients receiving lumasiran experienced substantial and sustained reductions in urinary oxalate, supporting the therapeutic hypothesis that RNAi mediated inhibition of glycolate oxidase may alleviate pathologic overproduction of oxalate in this devastating disease

Data support the continued development of lumasiran, with phase 3 study planned to initiate in mid-2018

- Alnylam also plans to study additional patients of younger ages and those with more severe manifestations of PH1, including renal failure and systemic oxalosis

Lumasiran Upcoming Presentations

European Society for Paediatric Nephrology (ESPN) Annual Meeting in Antalya, Turkey, October 4-6.

- Oral presentation on complete data from Phase 1/2 study of lumasiran (October 4)

American Society of Nephrology (ASN) Kidney Week Meeting in San Diego, CA, October 23-28.

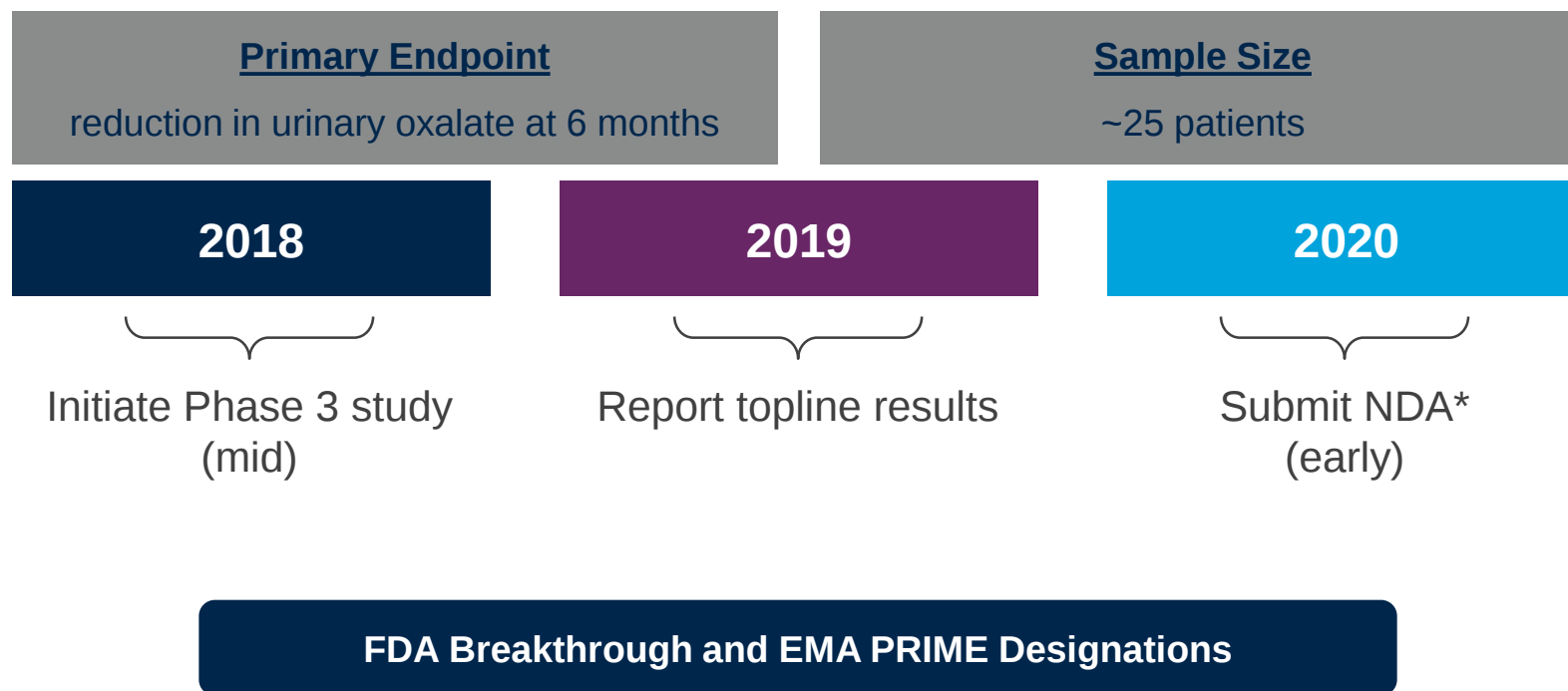
- Poster presentation on Phase 1/2 and open-label extension (OLE) study of lumasiran (October 25)

Lumasiran Phase 3 Study

Significant Acceleration in Advancement to Patients



Alignment reached on pivotal trial design



Agenda

Welcome

- Josh Brodsky, Director, Investor Relations & Corporate Communications

Introduction

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

Overview of Primary Hyperoxaluria Type 1

- Sally-Anne Hulton, M.D., FRCPCH, MRCP, FCP, MBBCh, Consultant Paediatric Nephrologist and Clinical Lead, Birmingham Children's Hospital NHS Trust

Patient Advocacy: Hyperoxaluria Patient Perspective

- Kim Hollander, Executive Director, Oxalosis & Hyperoxaluria Foundation

Lumasiran Program: Clinical Data and Next Steps

- Richard Riese, M.D., Ph.D., Vice President, Clinical Development
- Pritesh Gandhi, PharmD., Vice President, General Manager, Lumasiran

Q&A Session

Upcoming RNAi Roundtables

ONPATTRO™* & ALN-TTRsc02, for the Treatment of Transthyretin-Mediated Amyloidosis

- Tuesday, September 11

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company's website, www.alnylam.com/capella.



Thank You

