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

August 10, 2020

RNAi ROUNDTABLE 2020

Alnylam PHARMACEUTICALS

Agenda

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

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

Primary Hyperoxaluria Type I Background
- Michael J.G. Somers, M.D. – Associate Chief and Gunnar B. Stickler Chair in Pediatric Nephrology, Division of Nephrology and Medical Director, Renal Dialysis Unit, Boston Children's Hospital; Associate Professor of Pediatrics, Harvard Medical School; President, American Society of Pediatric Nephrology

Phase 1/2 OLE & ILLUMINATE Studies
- Tracy McGregor, M.D. – Sr. Director, Clinical Research

Program Opportunity in PH1
- 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: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by our products, or in patient enrollment in clinical trials, potential supply chain disruptions, and other potential impacts to our business, the effectiveness or timeliness of steps taken by us to mitigate the impact of the pandemic, and our ability to execute business continuity plans to address disruptions caused by the COVID-19 or any future pandemic; 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, including lumasiran, and our marketed products; intellectual property matters including potential patent litigation relating to our platform, products or product candidates; our and our partner's ability to obtain regulatory approval for our product candidates, including lumasiran and inclisiran, and our ability to maintain regulatory approval and obtain pricing and reimbursement for products, including ONPATTRO® (patisiran) and GIVLAARI® (givosiran); our progress in continuing to establish a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally, including ONPATTRO and GIVLAARI, and achieve net product revenues for ONPATTRO within our further revised expected range during 2020; our ability to successfully expand the indication for ONPATTRO in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses within the reduced ranges of guidance provided by us through implementation of further discipline in operations to moderate spend and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to establish and maintain business alliances, including completing an agreement for funding by Blackstone of certain R&D activities for vutrisiran and ALN-AGT; our dependence on third parties, including Novartis, for the development, manufacture and commercialization of inclisiran, Regeneron, for development, manufacture and commercialization of certain products, including eye and CNS products, Ironwood, for assistance with the education about and promotion of GIVLAARI, and Vir for the development of ALN-COV and other potential RNAi therapeutics targeting SARS-CoV-2 and host factors for SARS-CoV-2; the outcome of litigation; and the risk of government investigations; as well as those risks and other factors more fully discussed in our most recent annual, quarterly and current reports filed with the SEC. 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.

Agenda

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

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

Primary Hyperoxaluria Type I Background
- Michael J.G. Somers, M.D. – Associate Chief and Gunnar B. Stickler Chair in Pediatric Nephrology, Division of Nephrology and Medical Director, Renal Dialysis Unit, Boston Children's Hospital; Associate Professor of Pediatrics, Harvard Medical School; President, American Society of Pediatric Nephrology

Phase 1/2 OLE & ILLUMINATE Studies
- Tracy McGregor, M.D. – Sr. Director, Clinical Research

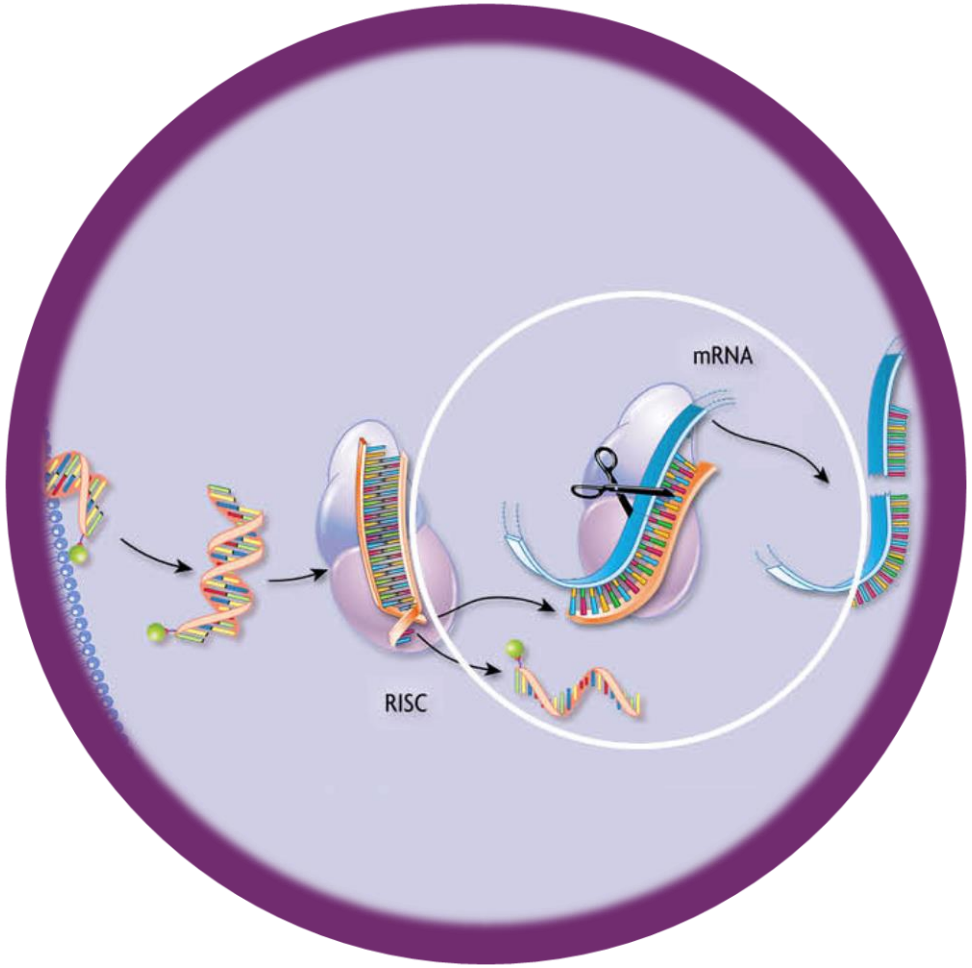
Program Opportunity in PH1
- Pritesh Gandhi, PharmD. – Vice President & General Manager, Lumasiran

Q&A Session

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 innovation**
- **Multiple products impacting patients globally**



Alnylam Commercial Products and Late Stage Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

		BREAKTHROUGH DESIGNATION	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION	COMMERCIAL	COMMERCIAL RIGHTS
onpattro (patisiran) lipid complex injection 10 mg/5 mL	*hATTR Amyloidosis*[1]	●			●	Global
GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL	*Acute Hepatic Porphyria*[2]	●			●	Global
Lumasiran	*Primary Hyperoxaluria Type 1*	●		●		Global
Inclisiran	*Hypercholesterolemia*			●		Milestones & up to 20% Royalties[3] **(Novartis)**
Patisiran	*ATTR Amyloidosis Label Expansion*		●			Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*		●			15-30% Royalties **(Sanofi)**
Vutrisiran	*ATTR Amyloidosis*		●			Global

[1] Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil 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

[2] Approved in the U.S. for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older

[3] As part of Blackstone strategic financing collaboration, 50% of inclisiran royalty revenue will be payable to Blackstone

As of August 2020

Alnylam Early Stage Clinical Development and 2020 IND Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	2020 IND CANDIDATES	EARLY STAGE *(Phase 1-Phase 2)*	COMMERCIAL RIGHTS
Cemdisiran	*Complement-Mediated Diseases*	✓			●	50-50 **(Regeneron)**
Cemdisiran/Pozelimab Combo[2]	*Complement-Mediated Diseases*				●	Milestone/Royalty **(Regeneron)**
ALN-AAT02 (DCR-A1AT)[3]	*Alpha-1 Liver Disease*	✓			●	Ex-U.S. option post-Phase 3 **(Dicerna)**
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*	✓			●	50-50 option post-Phase 2 **(Vir)**
ALN-AGT	*Hypertension*	✓			●	Global
ALN-HSD	*NASH*				●	50-50 **(Regeneron)**
ALN-COV (VIR-2703)	*COVID-19*			○		50-50 option post-Phase 2 **(Vir)**

2-4 *INDs per year planned from organic product engine*

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

[2] 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

[3] Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development

As of August 2020

Alnylam Commercial Products and Late Stage Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

		BREAKTHROUGH DESIGNATION	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION	COMMERCIAL	COMMERCIAL RIGHTS
onpattro (patisiran) lipid complex injection 10 mg/5 mL	*hATTR Amyloidosis*[1]					Global
GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL	*Acute Hepatic Porphyria*[2]					Global
Lumasiran	*Primary Hyperoxaluria Type 1*					Global
Inclisiran	*Hypercholesterolemia*					Milestones & up to 20% Royalties[3] **(Novartis)**
Patisiran	*ATTR Amyloidosis Label Expansion*					Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*					15-30% Royalties **(Sanofi)**
Vutrisiran	*ATTR Amyloidosis*					Global

[1] Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil 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

[2] Approved in the U.S. for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older

[3] As part of Blackstone strategic financing collaboration, 50% of inclisiran royalty revenue will be payable to Blackstone

As of August 2020

Primary Hyperoxaluria Type 1

Rare Genetic Disorder of Increased Endogenous Oxalate Synthesis

Primary Hyperoxaluria Type 1 (PH1):

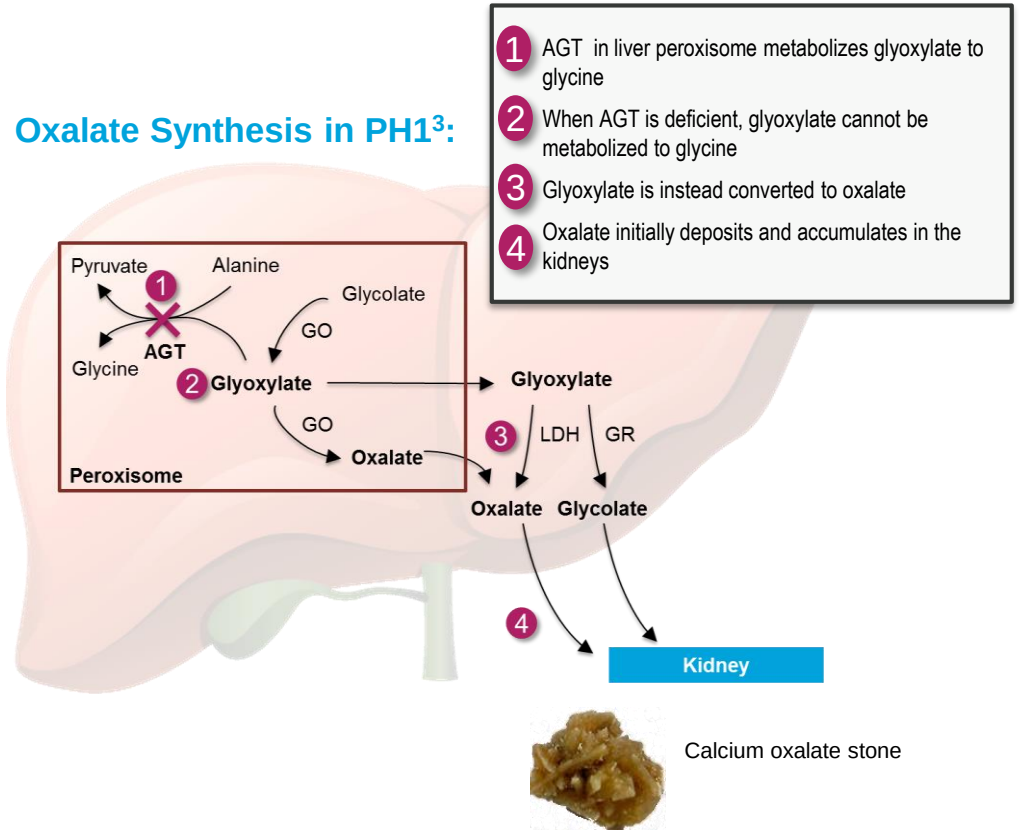
- Due to defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- Phenotype varies significantly in patients and may present at any age, typically in childhood
- Prevalence of PH1: 1-3/1,000,000 in Europe[1] and ~32/1,000,000 in Middle East[2]

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.

Agenda

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

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

Primary Hyperoxaluria Type I Background
- Michael J.G. Somers, M.D. – Associate Chief and Gunnar B. Stickler Chair in Pediatric Nephrology, Division of Nephrology and Medical Director, Renal Dialysis Unit, Boston Children's Hospital; Associate Professor of Pediatrics, Harvard Medical School; President, American Society of Pediatric Nephrology

Phase 1/2 OLE & ILLUMINATE Studies
- Tracy McGregor, M.D. – Sr. Director, Clinical Research

Program Opportunity in PH1
- Pritesh Gandhi, PharmD. – Vice President & General Manager, Lumasiran

Q&A Session

An Overview of Primary Hyperoxaluria and Oxalosis

Michael JG Somers, MD
Associate Chief
Division of Nephrology
Boston Children's Hospital
Harvard Medical School

Boston Children's Hospital
Until every child is well℠

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Setting the Stage: Case One

Presentation as an infant

- A two-month-old previously healthy girl develops several days of spitting up and some diarrhea
- She is brought for evaluation and found to have severe kidney failure (creatinine 9.3 mg/dL) and starts peritoneal dialysis
- Her initial evaluation is negative other than echogenic or bright appearing kidneys on ultrasound
- An ultrasound after nearly a year of dialysis shows calcified kidneys, and she is referred for more specific evaluation
- A diagnosis of hyperoxaluria (PH1) is made by genetic analysis
- She starts six day a week hemodialysis at 14 months of age
- She undergoes successful liver-kidney transplant at 20 months of age

Setting the Stage: Case Two

Presentation as an adolescent

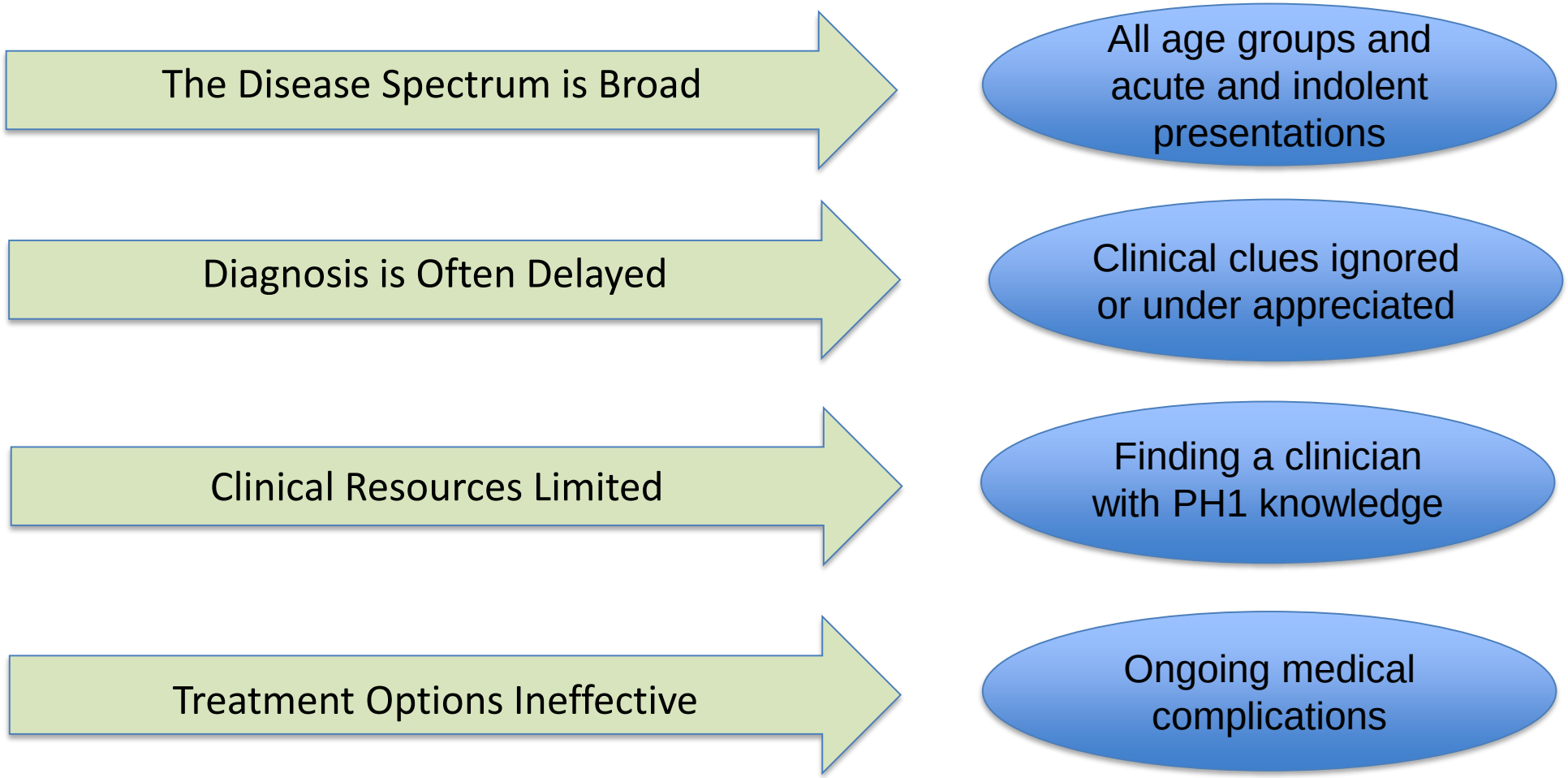
- A 13-year-old previously healthy boy develops several days of increasingly severe flank pain
- He is brought for evaluation and found to have kidney stones in both kidneys, calcium deposits in both kidneys, and kidney function that is decreased to 60% of normal
- A diagnosis of PH1 is suspected from urine studies and then confirmed after a liver biopsy
- Over the next 12 years, he requires nearly 20 urologic procedures or admissions for his kidney stones, with declining kidney function
- He starts six time a week hemodialysis at age 25 years
- He undergoes successful liver-kidney transplant at age 26 years

Setting the Stage: Case Three

Presentation as an adult

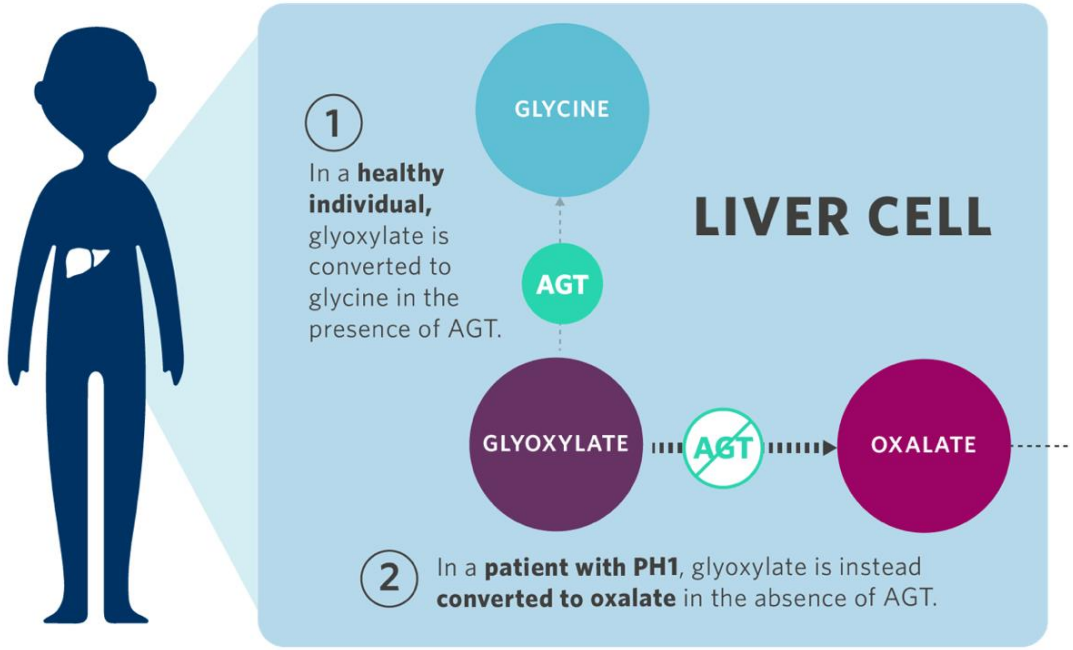
- A 25-year-old graduate student is referred because of recurrent kidney stones and newly detected abnormal kidney function
- She has been developing stones since college and has seen several urologists who have removed stones and told her to drink more
- Urine collections point towards a diagnosis of PH1, confirmed by genetic testing
- Very high urinary oxalate levels drop after starting pyridoxine
- After five years, she has not had further kidney stones
- Her kidney function has been slowly declining and is now 20% of normal
- She has started an evaluation for a kidney transplant

Primary Hyperoxaluria:
Common Themes in Clinical Cases



Understanding PH1:

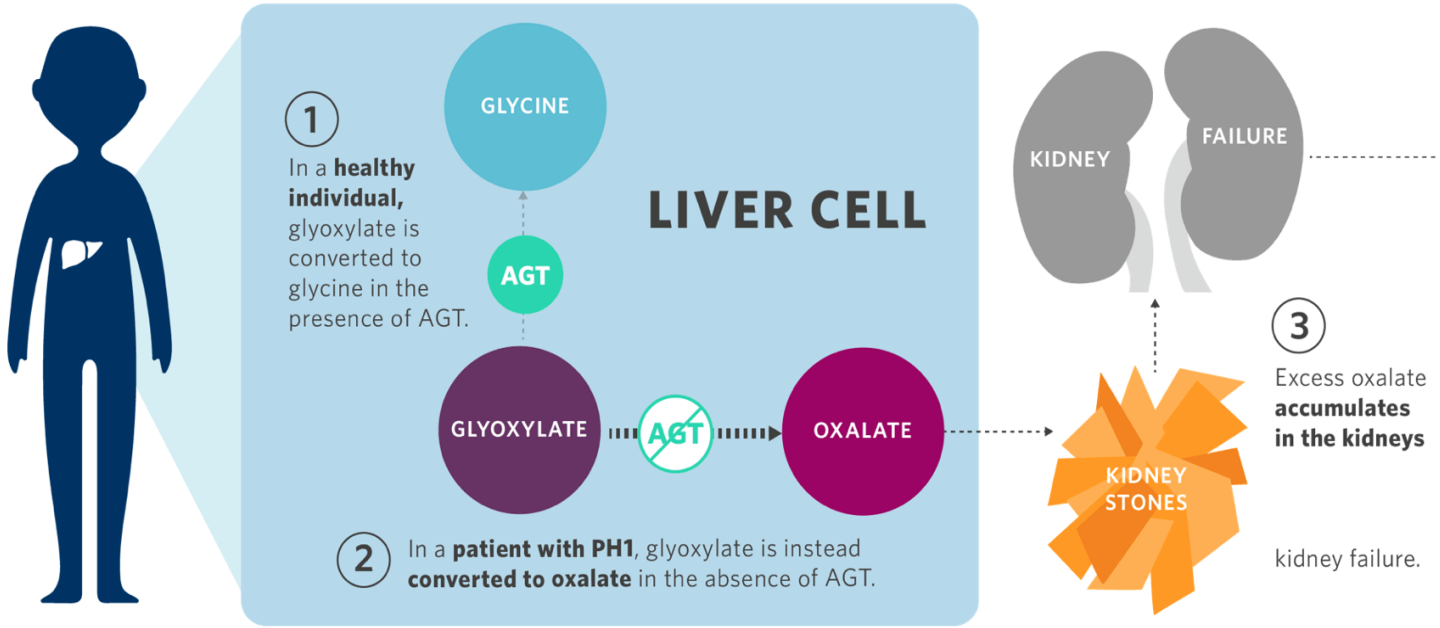
The Initial Problem Lies with the Liver



- With hyperoxaluria, inborn errors in hepatic metabolism result in enhanced oxalate production
- There are three primary forms of hyperoxaluria, but PH1 accounts for 80% of cases
- In PH1, the hepatic peroxisomal enzyme AGT is absent or ineffective due to mutations in the AGXT gene
- Large oxalate burdens get generated throughout life

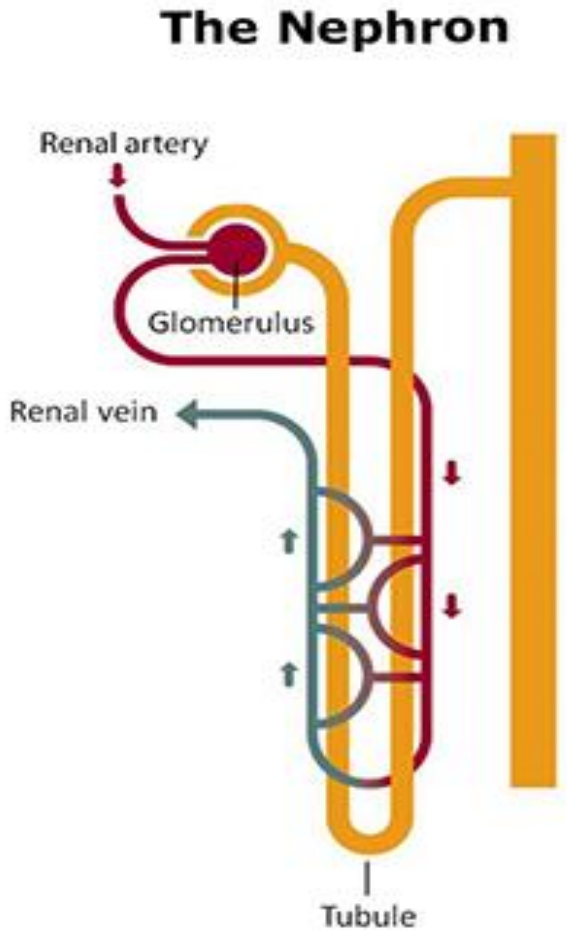
Understanding PH1:

The Kidney Gets Involved



- The kidney eliminates excess oxalate from the body in the urine
- Large oxalate loads cause nephrolithiasis (kidney stones) and nephrocalcinosis (calcium deposition in the kidney tissue)
- Ongoing oxalate-mediated injury to the kidney eventually leads to progressive loss of kidney function

Some Important Kidney Information

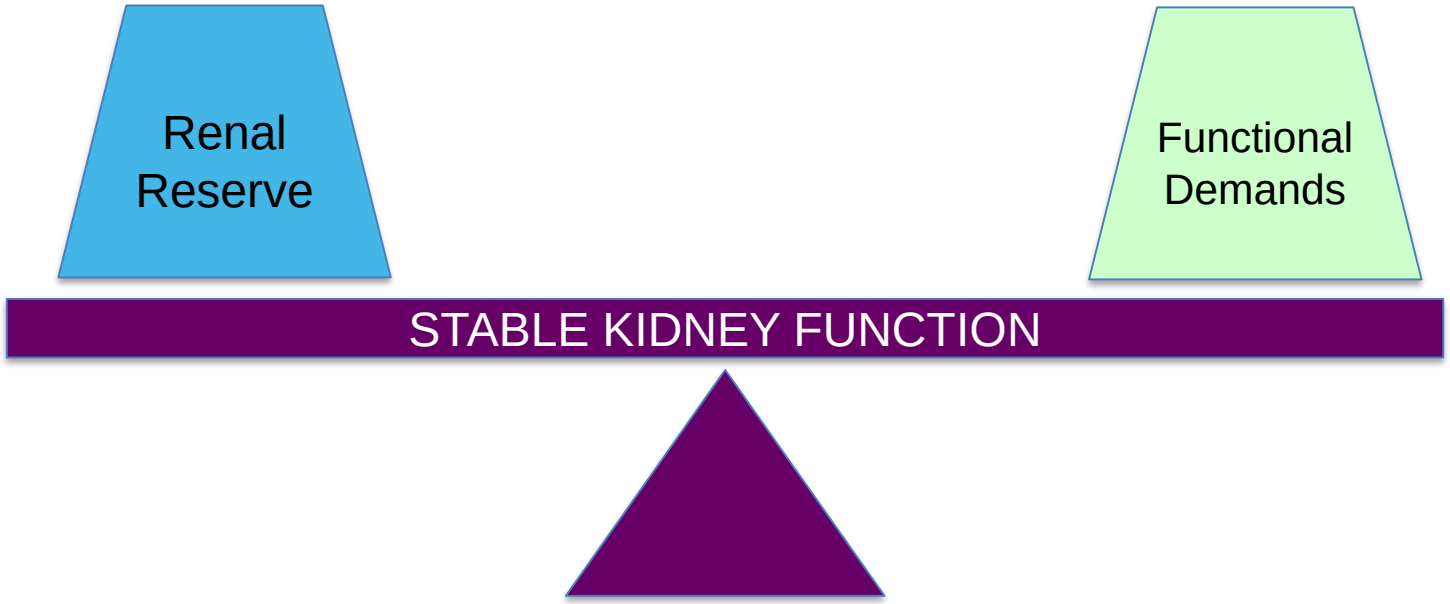


https://www.niddk.nih.gov/health-information/kidney-disease/kidneys-how-they-work

- The building block of the kidney is called the nephron – each nephron consists of a glomerulus that filters the blood and a tubule that fine tunes the filtrate
- Normal kidney development results in upwards of a million nephrons formed before birth, with no further nephron development ever happening during life
- All nephrons have some inherent tendency towards obsolescence or wearing out
- Adequate kidney function depends on there being enough functioning nephrons

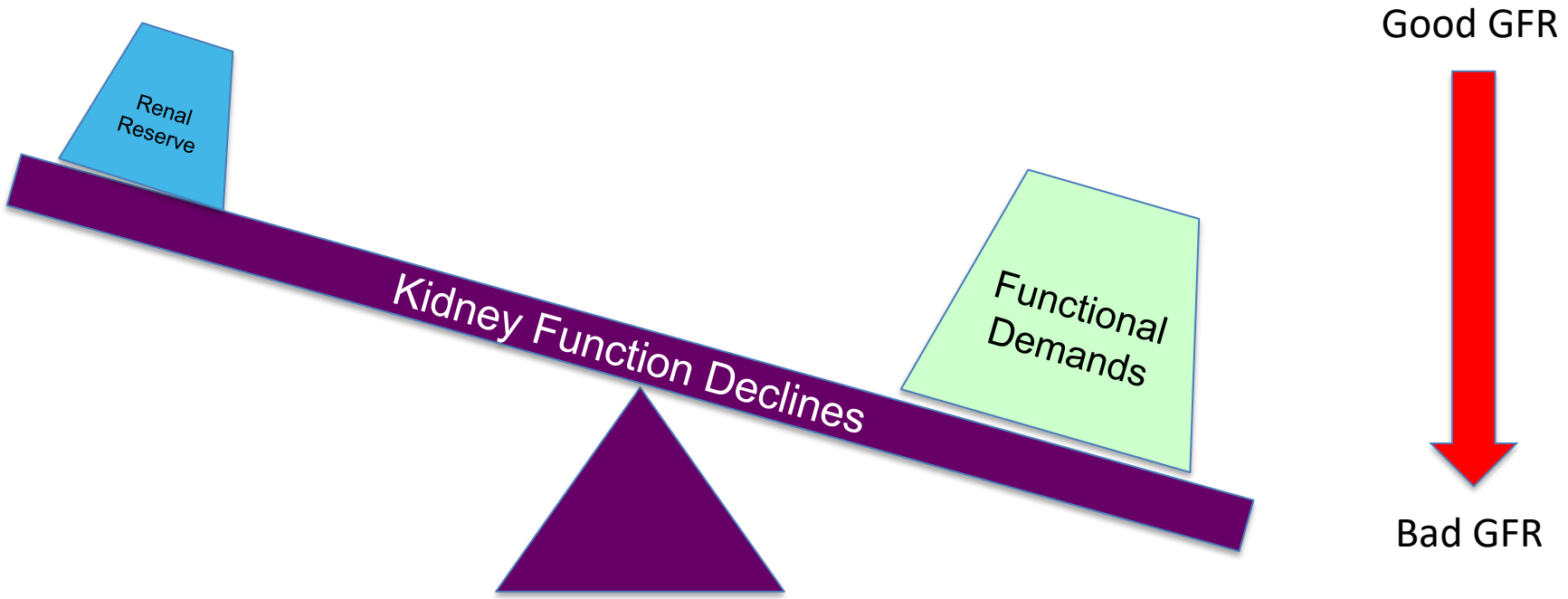
Overview: Renal Function

Renal functional capacity is directly related to renal reserve. A stable reserve will result in maintained kidney function throughout life.

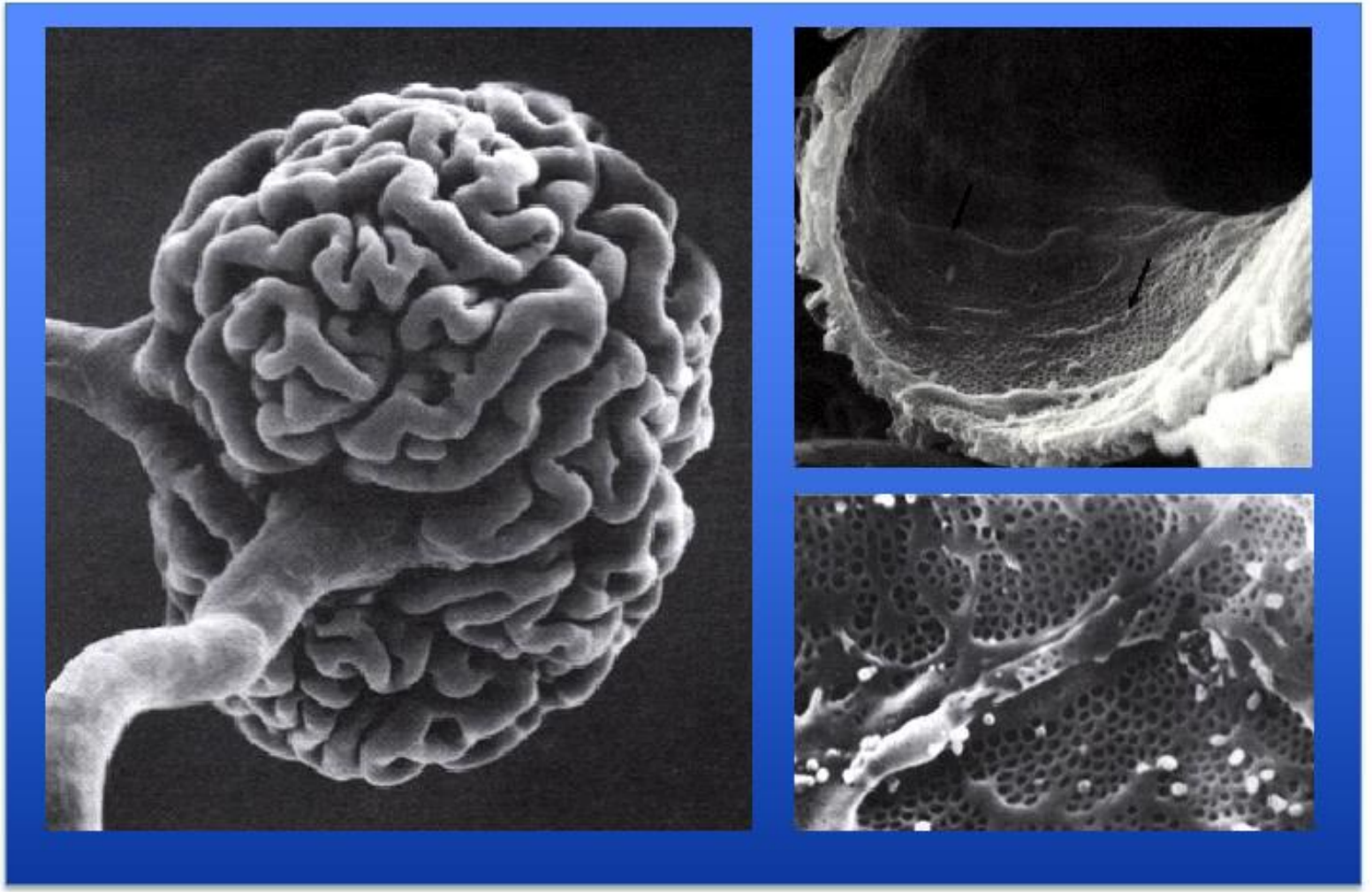


Overview: Renal Function

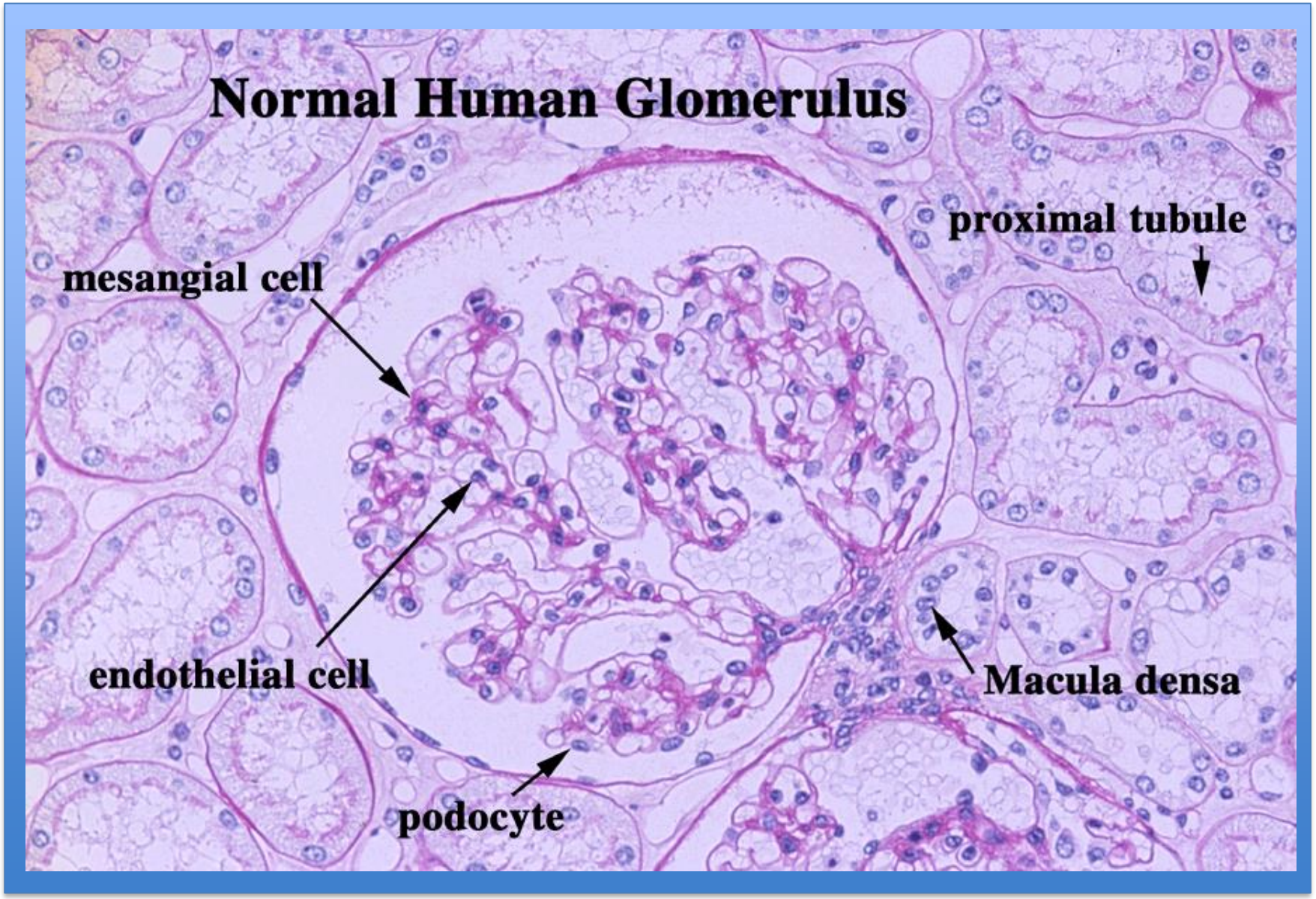
Loss of renal reserve means that long-term functional capacity may be compromised if compensatory mechanisms cannot be maintained. New renal insults may also adversely affect reserve and hasten loss of function.



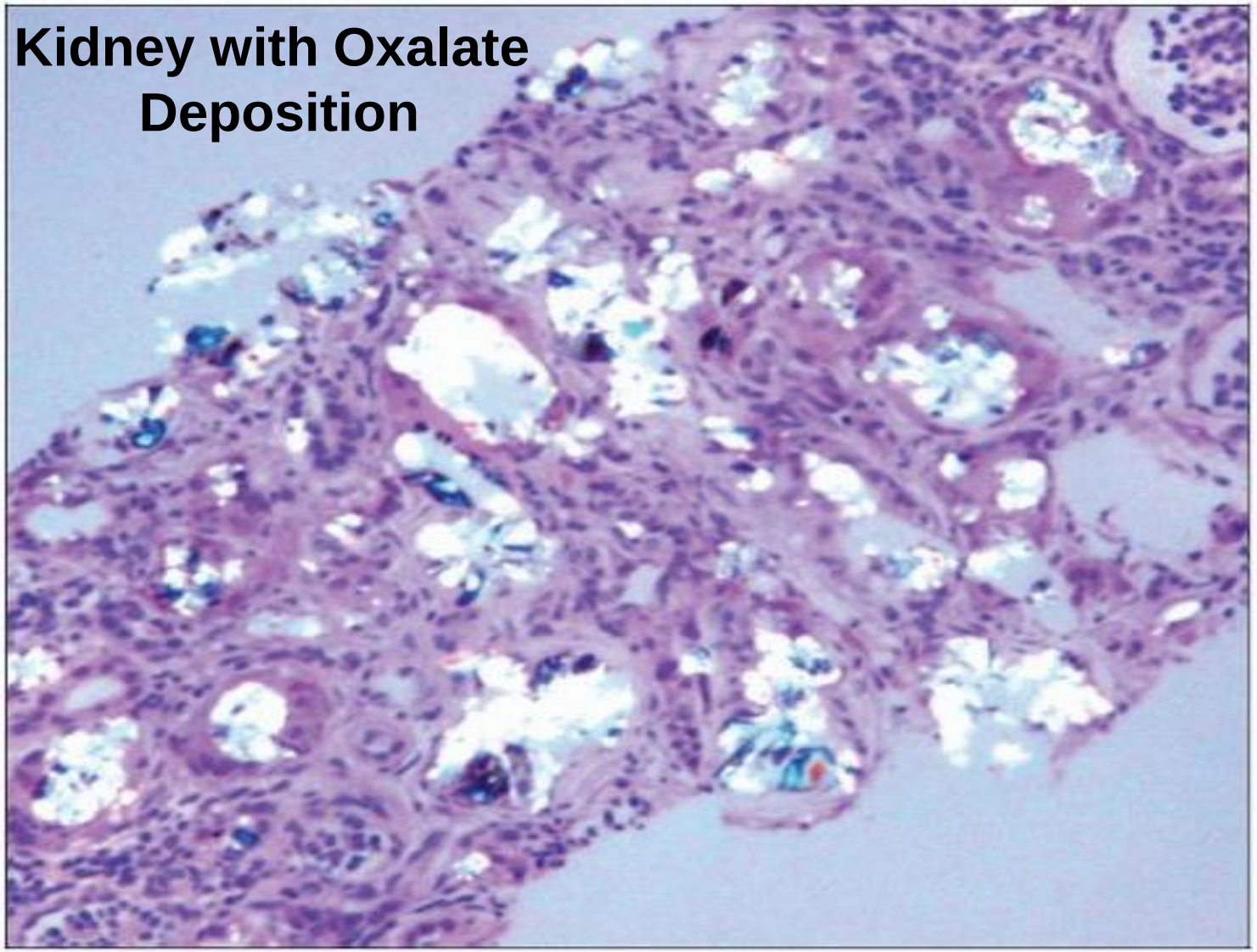
GFR = glomerular filtration rate



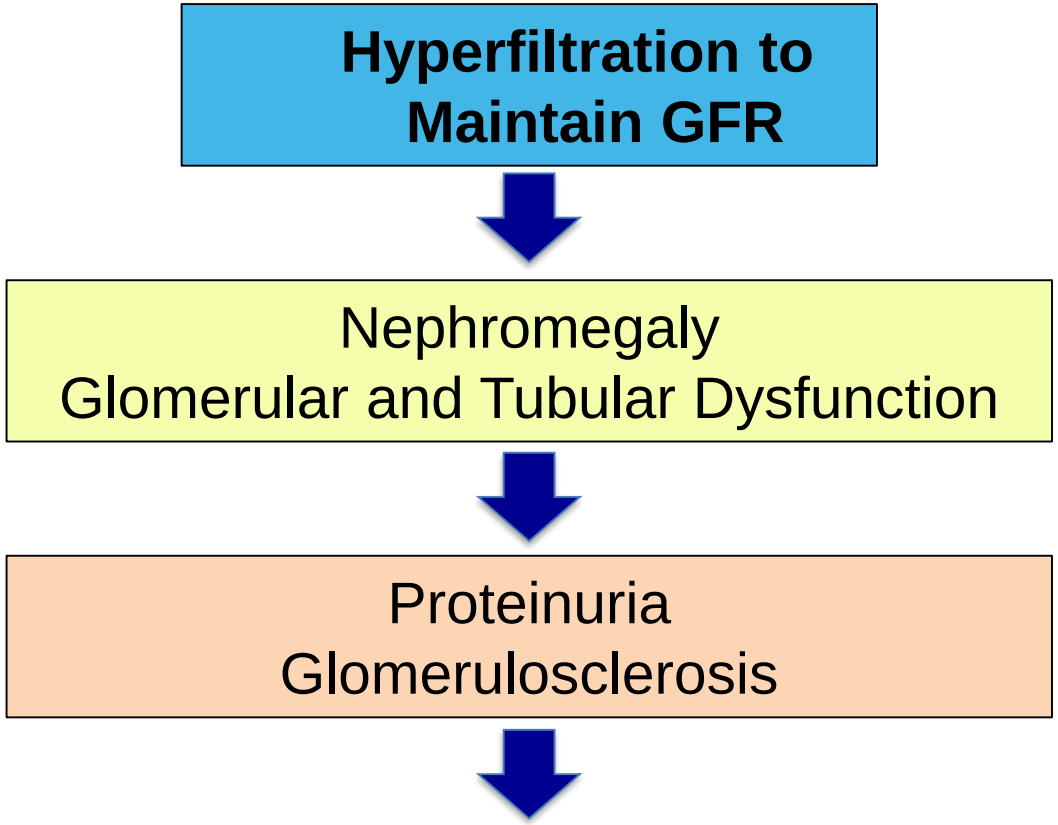
from Brenner & Rector, The Kidney, W.B.Saunders; Heptinstall, Pathology of the Kidney, Little, Brown & Co.; Seldin & Giebisch, The Kidney, Lippincott, Williams & Wilkins; and Tryggvason (1999) JASN 10:2440.


Normal Human Glomerulus
mesangial cell
proximal tubule
endothelial cell
Macula densa
podocyte

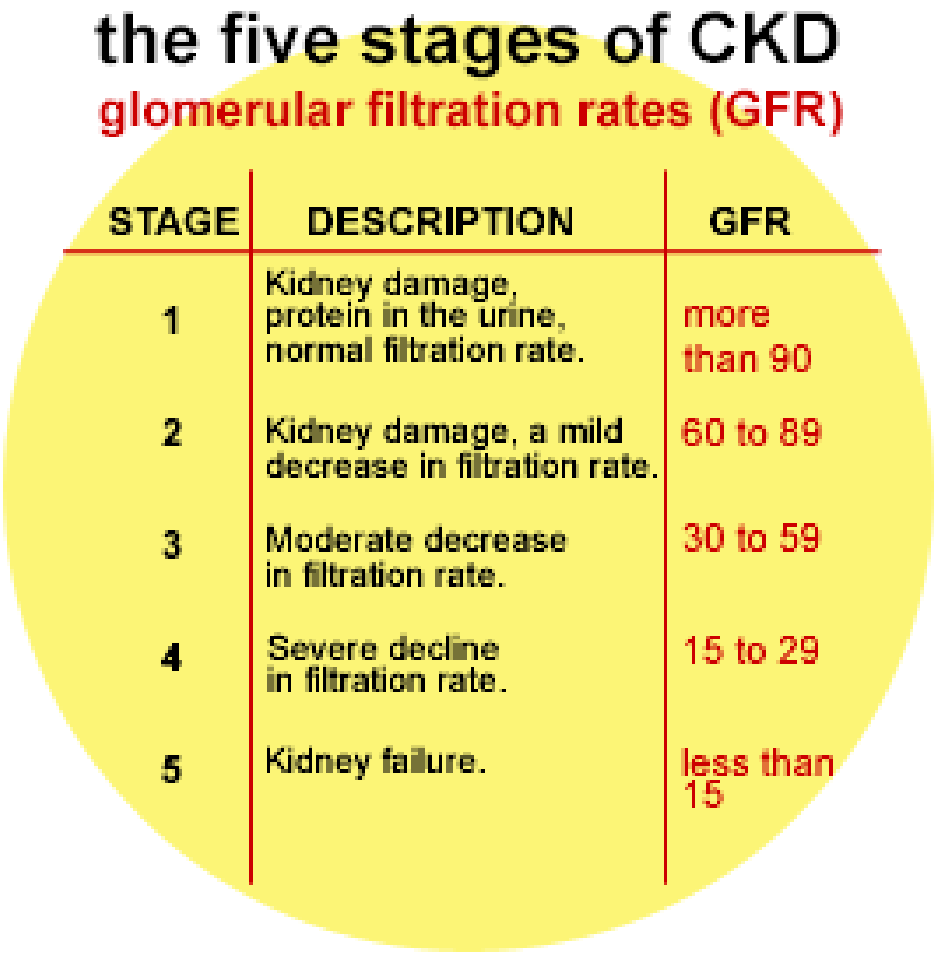
Kidney with Oxalate Deposition



Reduced Renal Reserve:
Consequences of Oxalate Injury



Chronic Kidney Disease Tends to be Progressive



The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOCI) provides clinical practice guidelines for all phases of kidney disease and related complications.

- Loss of glomerular reserve mediates loss of kidney function
- Tendency to progress through stages of Chronic Kidney Disease to End Stage Kidney Disease (ESKD)
- **ESKD means need for chronic renal replacement therapy**

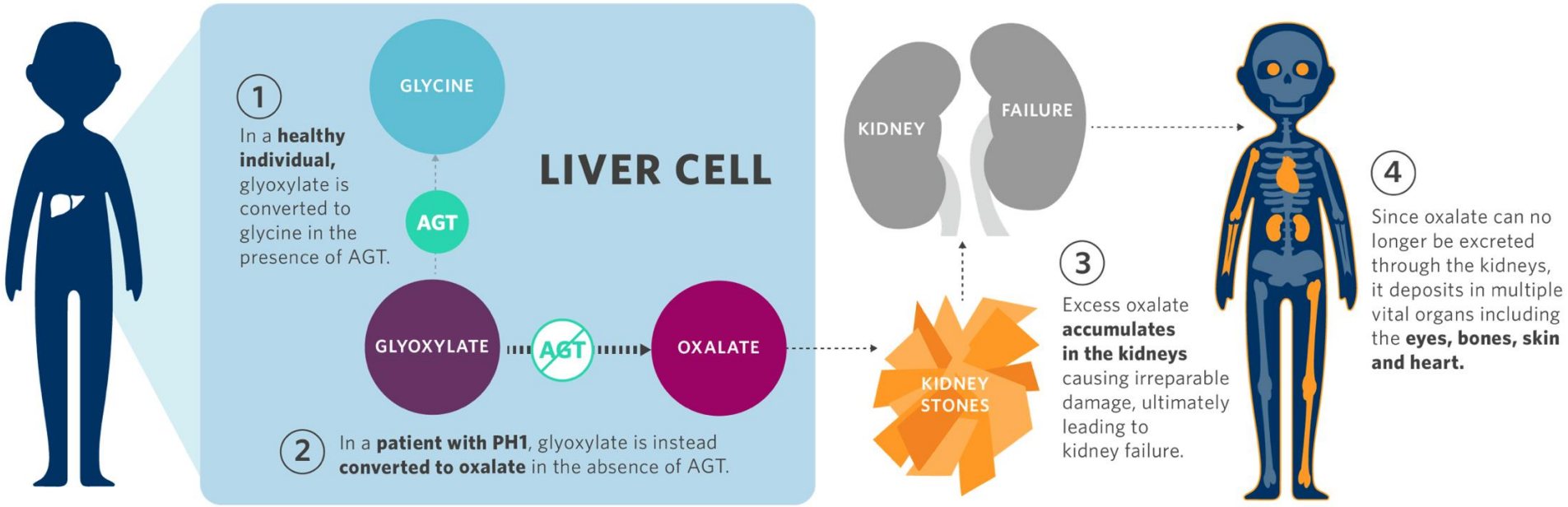
Chronic Kidney Disease: Progression

CKD Stage	GFR
1	≥ 90
2	60-89
3	30-59
4	15-29
5 (ESKD)	< 15

Dialysis and Transplant

- Interventions to prevent disease progression need to happen early in the course of chronic kidney disease
- After a certain number of filtering units are lost, there is ***inevitable progression***
- With lower kidney function, this needs to be kept in mind in terms of new therapies and expectation for cures

Kidney Failure Exacerbates the Consequences



- As kidney function falls to less than 50%, the ability to eliminate excess oxalate produced also declines
- Oxalate then starts getting deposited in tissues outside of the kidney, notably in the bone, eyes, heart, and skin
- Oxalosis is this state of systemic oxalate deposition with even more profound adverse health consequences

PH1: Basic Demographics

PH1 Epidemiology	
Prevalence	• 1-3/1,000,000
Incidence	• 1-2/10,000,000
Proportion of Pediatric ESKD	• 1-2%
Proportion of all cases of PH	• 75-80%

- Frequency rate is higher in geographically isolated or in consanguineous populations
- Underdiagnosis likely skews frequency estimates
- Population analysis from the NHLBI Exome Sequencing Project estimates PH1 prevalence of 1:149,000 in European Americans and 1:157,000 in African Americans

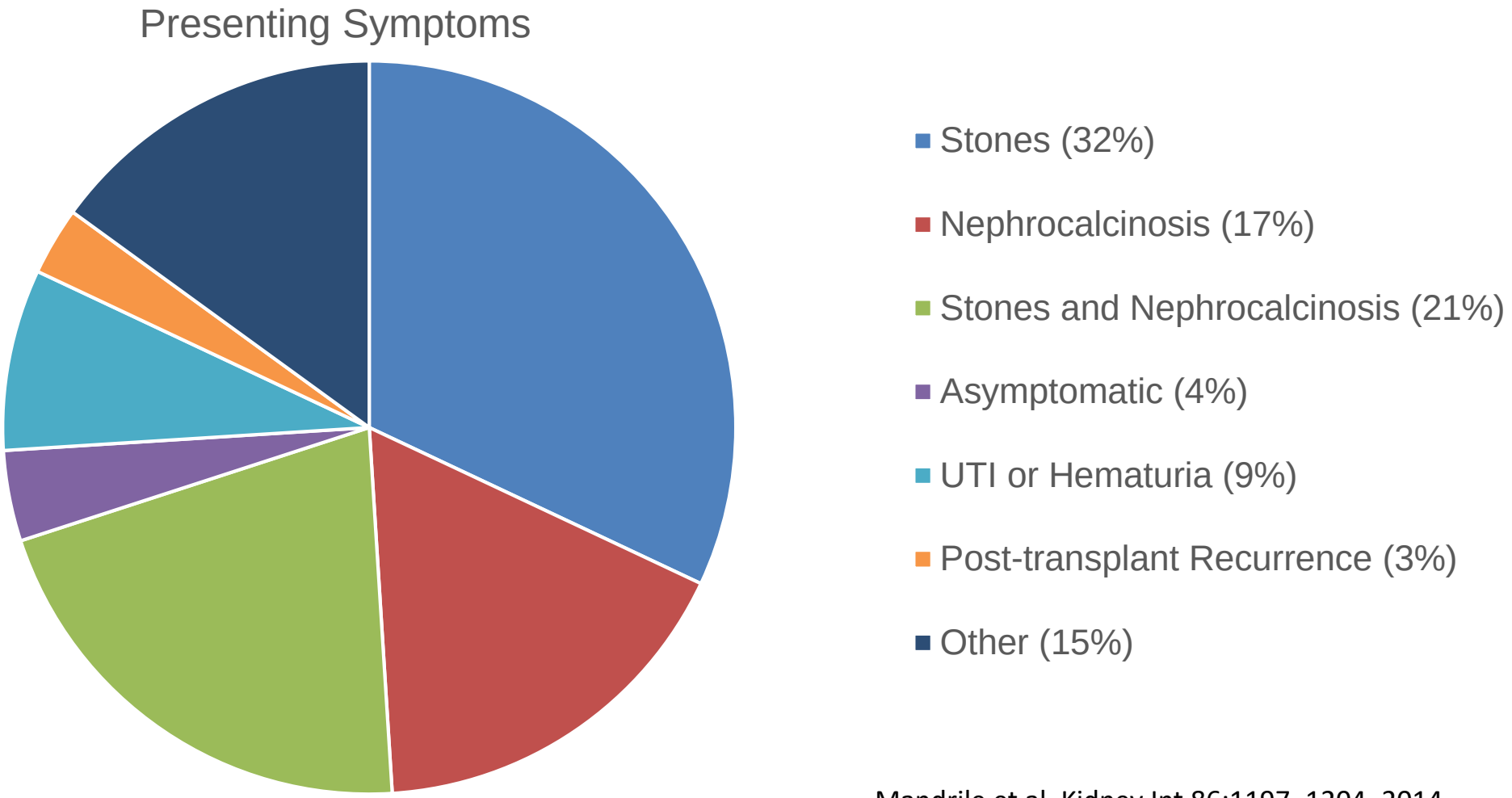
PH1: Renal Phenotype

Kidney Manifestations	Frequency
Early nephrolithiasis and nephrocalcinosis with renal failure in infancy	• 10%
Recurrent nephrolithiasis with renal failure in childhood, adolescence, or as young adult	• 65%
Diagnosis after ESKD due to systemic oxalosis on dialysis or recurrence in a transplant	• 10%
Late onset of nephrolithiasis as an adult	• 7.5%
Diagnosis prior to symptoms because of screening	• 7.5%

Estimated frequencies are based largely on data from registries of PH patients receiving care in North America or Europe and may be skewed

Miiliner et al, Gene Reviews, 2017

Symptoms Leading to Diagnosis in PH1 Patients

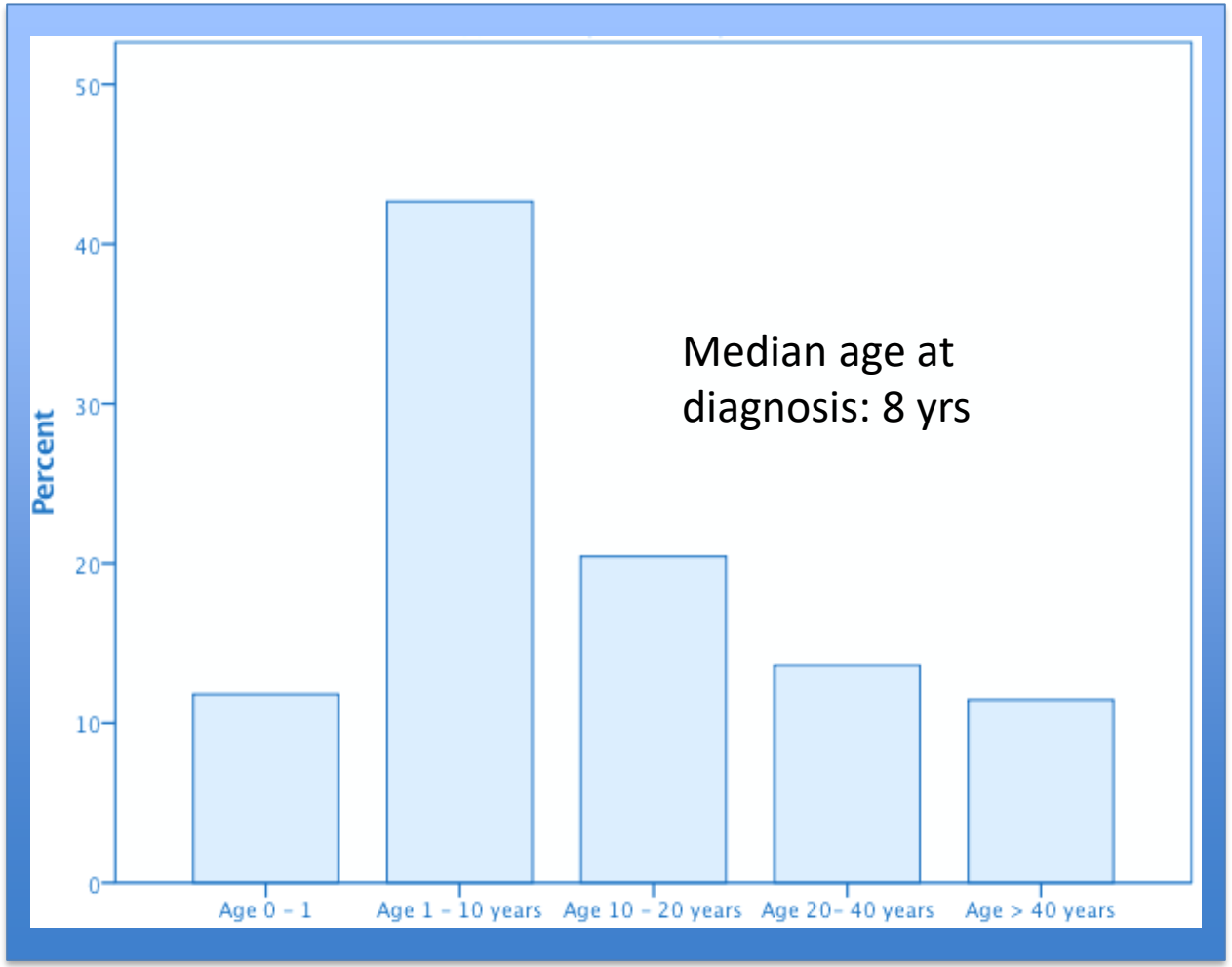


Mandrile et al, Kidney Int 86:1197–1204, 2014

Notable Features in PH1

CLINICAL FEATURES AT DIAGNOSIS	
Infantile onset is common	Up to a third of affected patients have symptoms as an infant. In a third of affected infants, they have ESKD at presentation.
Diagnosis during childhood is typical	Outside of infancy, a diagnosis between 5-10 years of age is common
ESKD is common at time of diagnosis	In some cohorts, 40% or more of patients have ESKD by the time a diagnosis is made
Delayed diagnosis	Most patients have had missed opportunities for early diagnosis related to prior symptoms

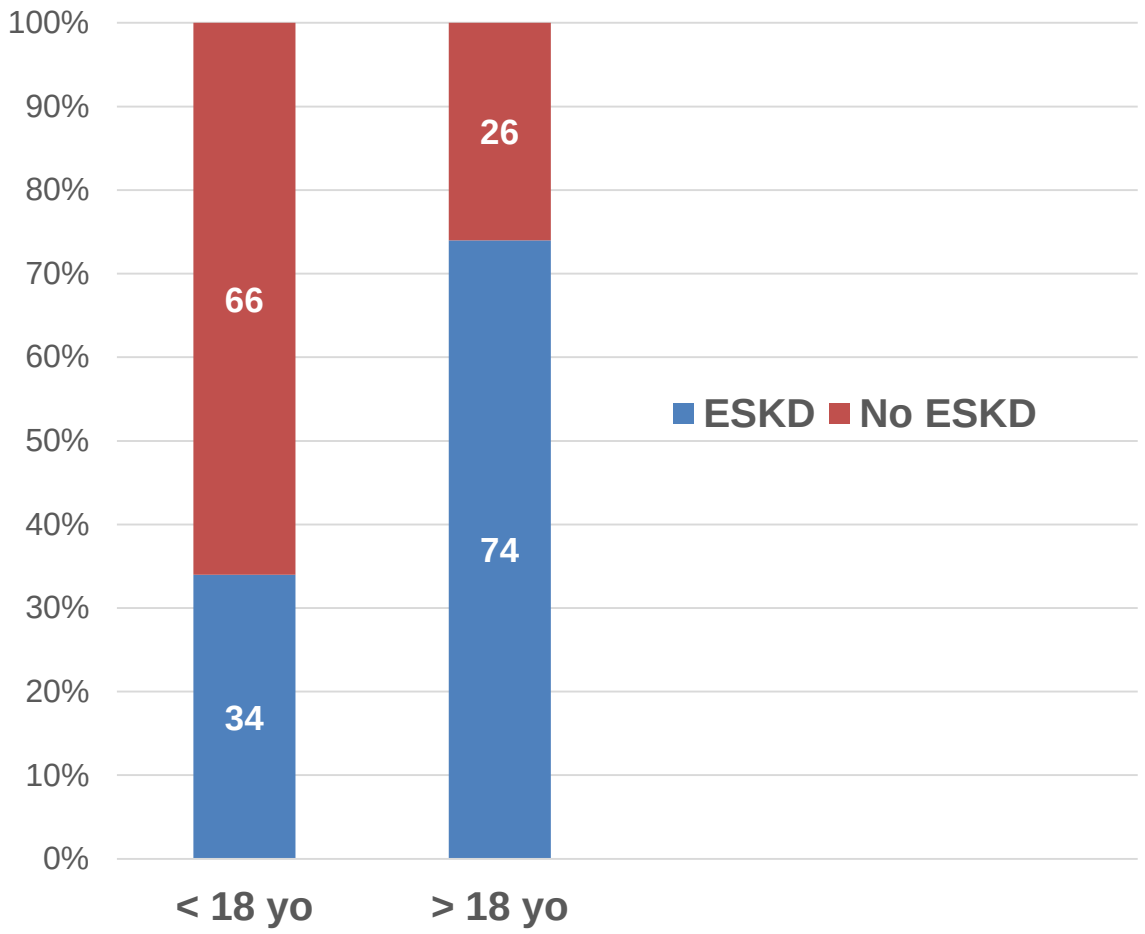
Age at Diagnosis in PH1



- Most patients are diagnosed early in life, but 70% after more than a year of symptoms
- Those patients diagnosed as adults are more likely to already have ESKD or very advanced loss of kidney function due to duration of hyperoxaluria

OxalEurope data

ESKD at Diagnosis in PH1

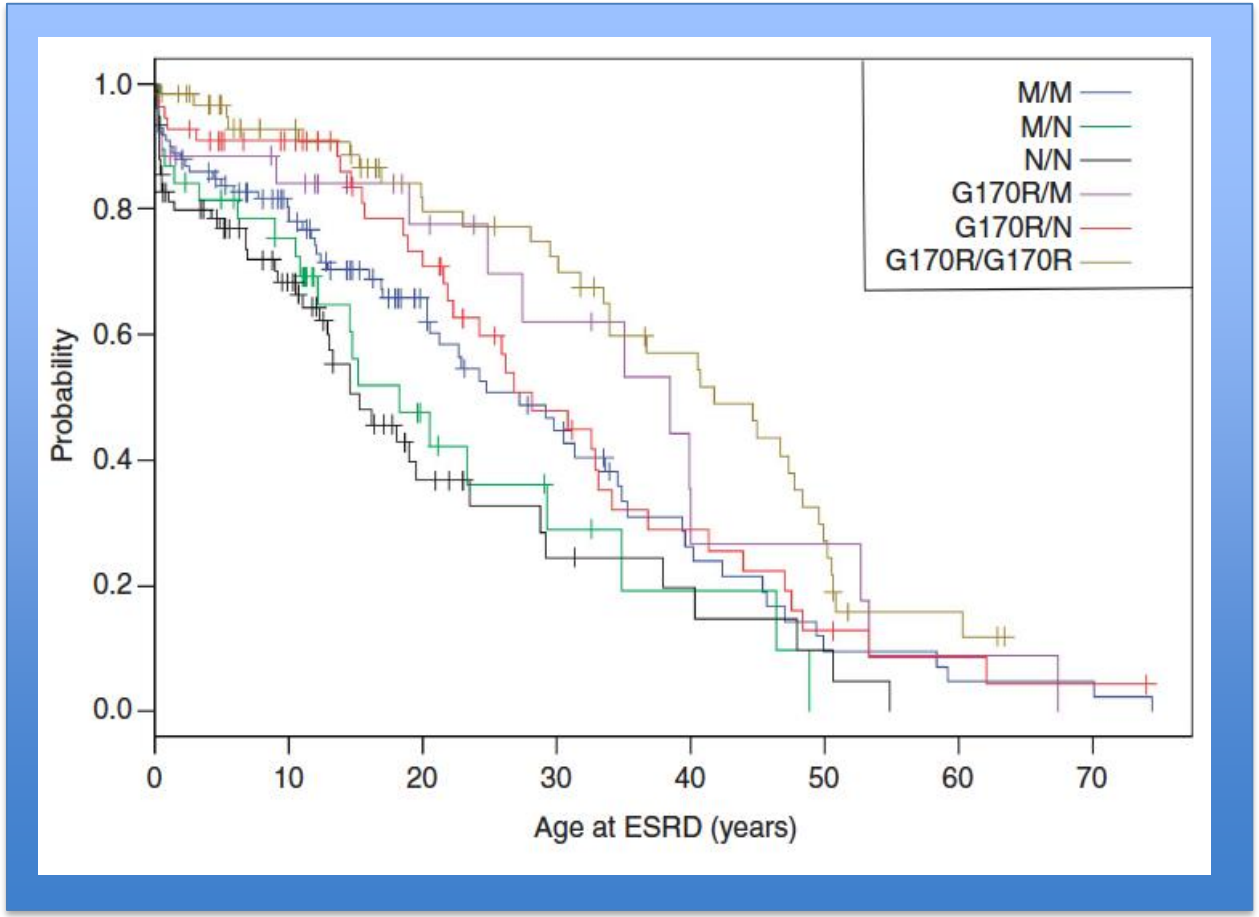


- Younger patients at diagnosis are more likely to still have enough renal function to forgo immediate renal replacement therapy
- Longer periods of poor kidney function and longer periods of hyperoxaluria predispose to more adverse consequences of oxalosis and poorer kidney function at diagnosis in older patients

OxalEurope data

Time to ESKD in PH1 Patients

Variations by Genotype

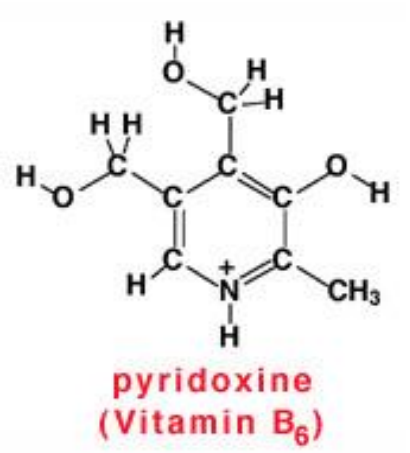


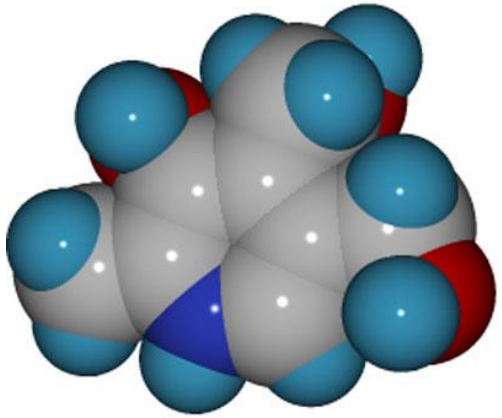
- Nearly 200 mutations in AGXT gene leading to PH1 have been described
- Mutations are classified as null (no AGT produced) or missense (AGT produced but cannot be used)
- Presence of at least one G170R mutation slows down progression to ESKD

Mandrile et al, Kidney Int 86:1197–1204, 2014

Genotypes in PH1 Patients

Pyridoxine Sensitivity





- About 30% of PH1 patients have a G170R mutation
- Affected individuals with this mutation benefit from treatment with pyridoxine (vitamin B6)
- With this mutation, AGT is produced but is “mis-targeted” and delivered to wrong cellular compartment of the liver cell
- Pyridoxine helps to stabilize the AGT, increase its enzymatic strength, and improve its delivery to the right cellular compartment in the liver
- Abnormal oxalate production can be substantially blunted with PH1 caused by this mutation with pyridoxine therapy

http://www.chemistry.wustl.edu/~edudev/LabTutorials/Vitamins/pyridoxine.htm

Best Practices: Diagnosis

Who Should be Considered for a PH Diagnosis?
Stones or nephrocalcinosis in childhood
Recurrent calcium oxalate stones as an adult
Nephrocalcinosis as an adult
Family history of hyperoxaluria
Decreased kidney function with history or stones or nephrocalcinosis
ESKD of unclear etiology

Best Practices: Diagnostic Evaluation

How is PH1 diagnosed?	
Urinary oxalate studies	• Urine oxalate >0.7 mmol/1.73 M2/day • Urine oxalate/creatinine ratio abnormal
Genetic testing	• AGXT Gene Analysis
Plasma oxalate	• Levels > 20 umol/L may be suggestive with advanced CKD or ESKD
Liver biopsy	• Direct assessment of AGT activity but rarely needed in era of genetic testing

Best Practices: Supportive Management

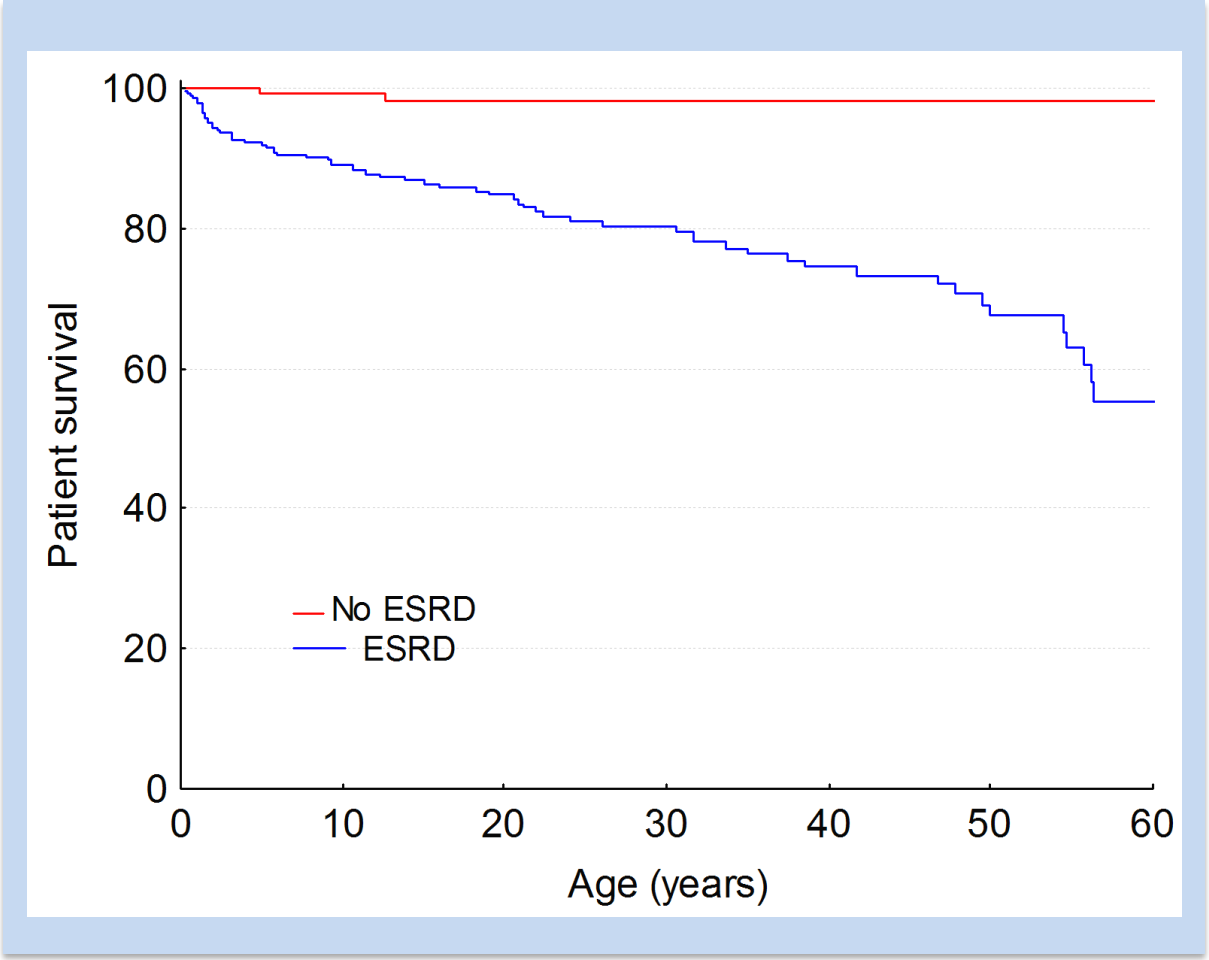
CONSIDERATIONS FOR THE PATIENT	
Pyridoxine	Should be given until genetic testing results known with consideration of effects on 24hr urine oxalate levels
Medications	Use of citrate, phosphate, magnesium to help prevent oxalate crystal formation
Hydration	Hyperhydration of 2.5 to 3 liters/M2/day – episodes of dehydration can be catastrophic, especially if accompanied by acute drop in GFR

Best Practices: Supportive Management

CONSIDERATIONS FOR THE PATIENT	
NG or G-tube	Needs to be discussed early and benefits clearly outlined
Dietary vigilance	Decrease any factors that may be increasing enteric oxalate absorption, avoid high oxalate foods, be judicious with dietary sodium
Urinary tract management	Role of urologist with understanding of hyperoxaluria
Center expertise	Need medical resources familiar with management of PH1 through CKD to ESKD

Mortality in PH1 Patients

ESKD Markedly Reduces Lifespan

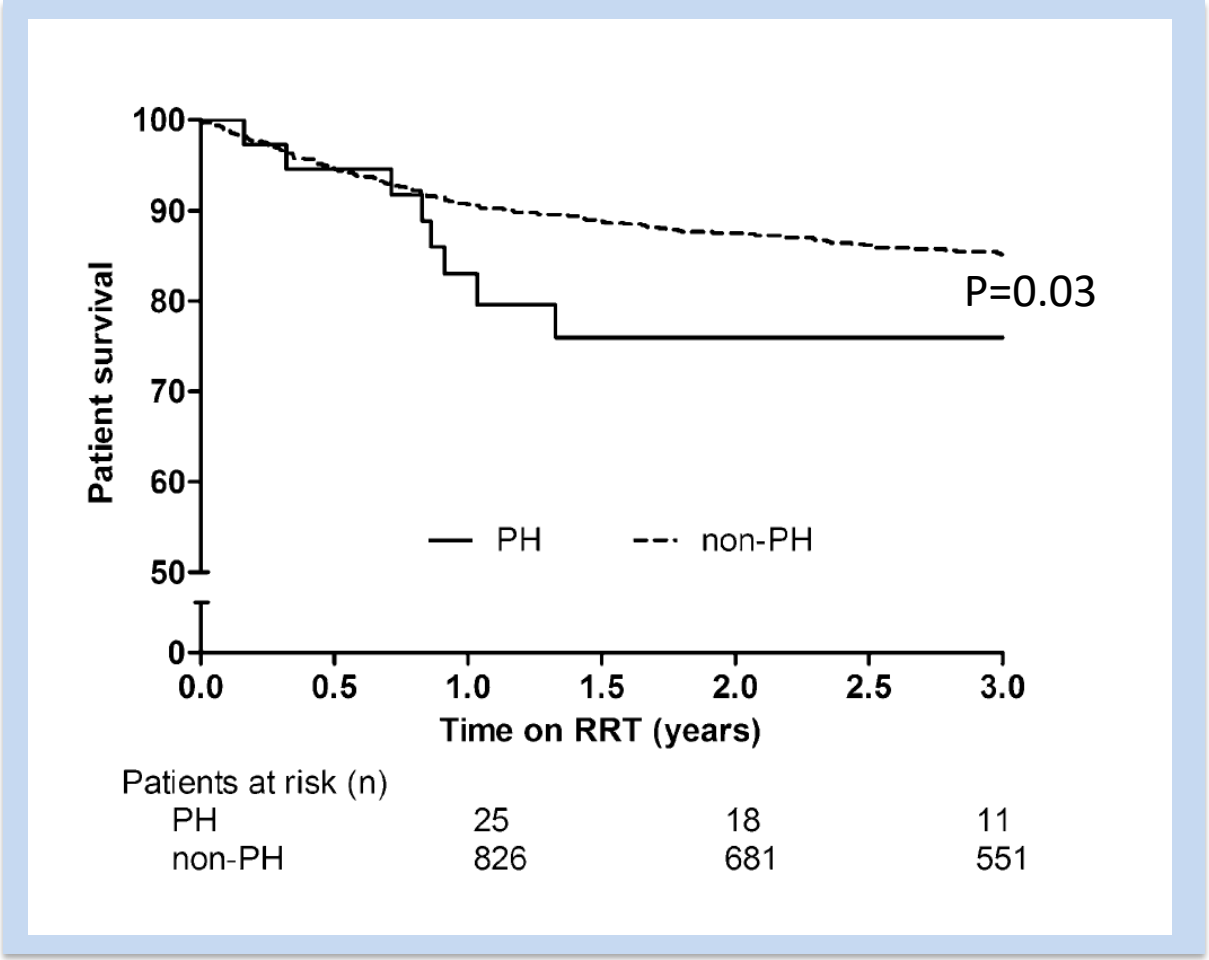


Individuals with PH who do not progress to ESKD have improved mortality vs those with ESKD

Harambat and OxalEurope data

Mortality in PH1 Patients

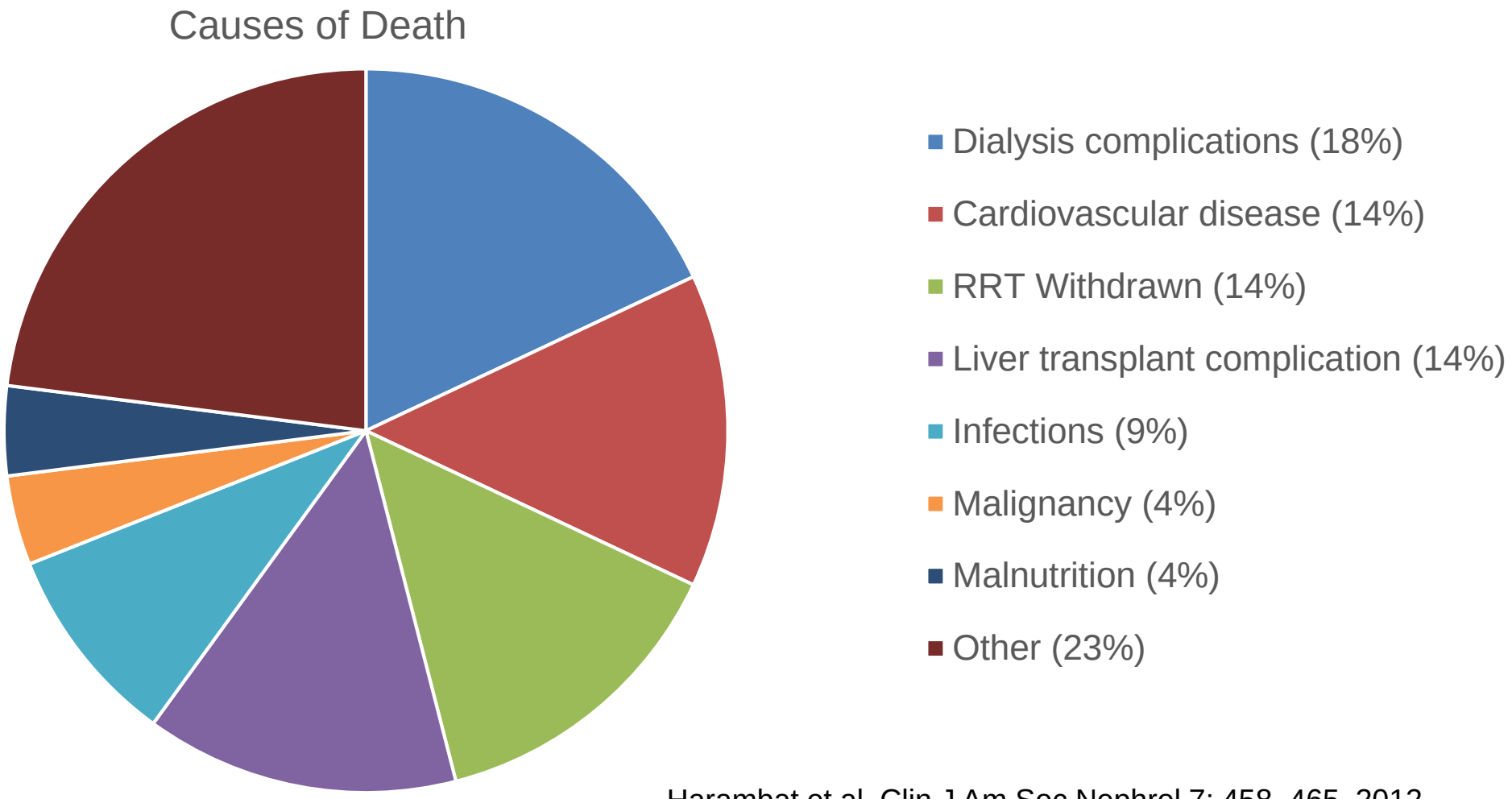
During Renal Replacement Therapy



Survival on RRT with PH as a primary diagnosis is significantly lower than survival with another etiology of ESKD

Harambat et al, Clin J Am Soc Nephrol 7: 458–465, 2012

Mortality in PH1 Patients
During Renal Replacement Therapy



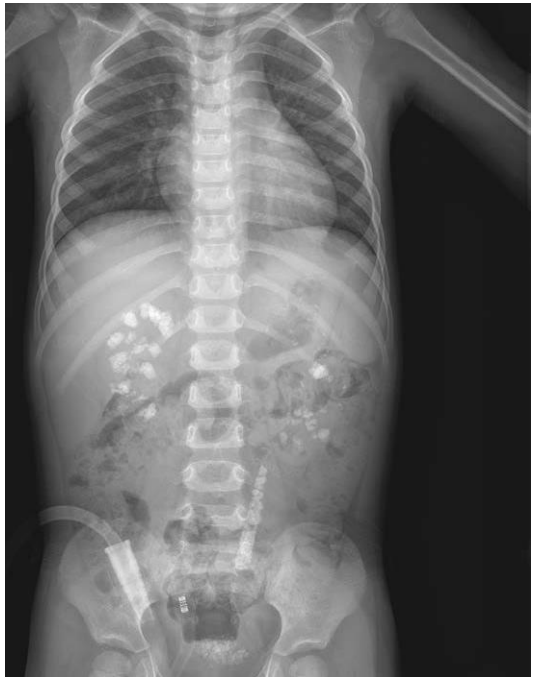
Harambat et al, Clin J Am Soc Nephrol 7: 458–465, 2012

Oxalosis

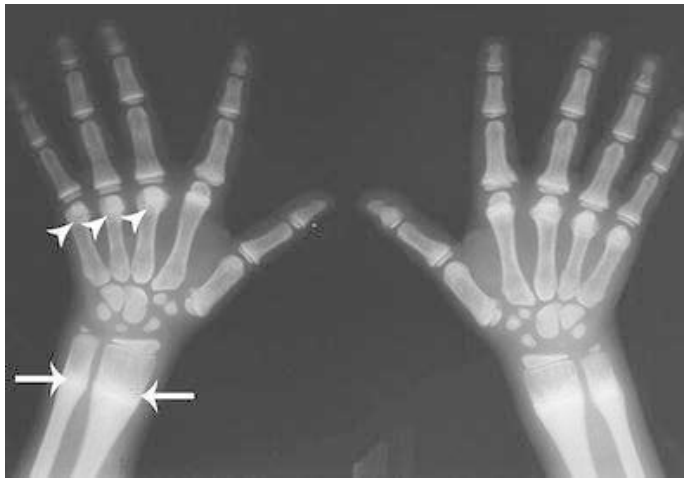
Multiorgan System Involvement			
Kidney	•	stones, nephrocalcinosis, ESKD	Always
Bone	•	fractures, bone pain, poor growth	Very frequent
Eye	•	retinal deposits with visual impairment	Very frequent
Heart	•	cardiac failure, arrhythmias	Often
Arteries	•	calcification of the blood vessel walls	Often
Thyroid	•	decreased function	Often
Skin	•	nodules, gangrene, itching, livedo	Ongoing risk
Muscle	•	myopathy	Ongoing risk
Nerves	•	neuropathy	Ongoing risk

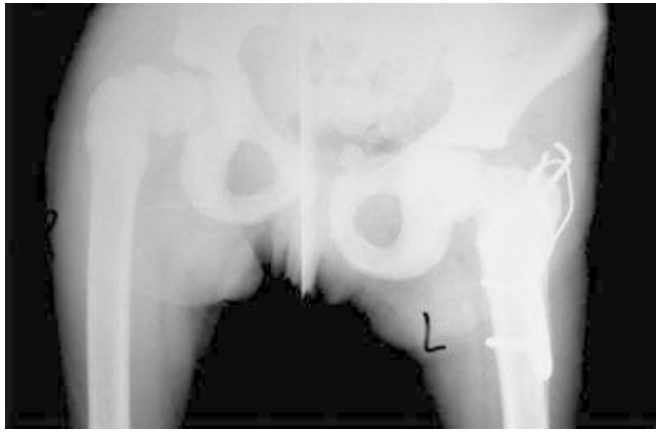
Disease burden can be overwhelming

Systemic Findings with PH1

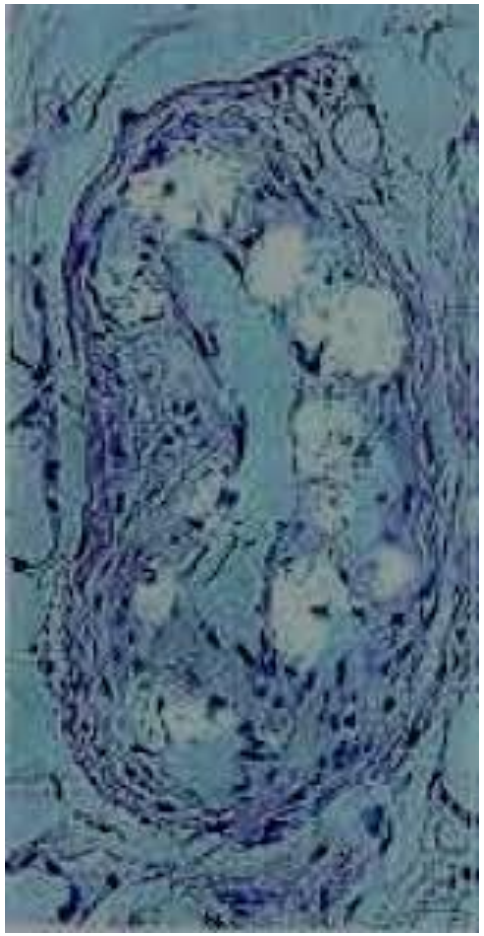


Jiang et al, N Engl J Med 376:15, 2017



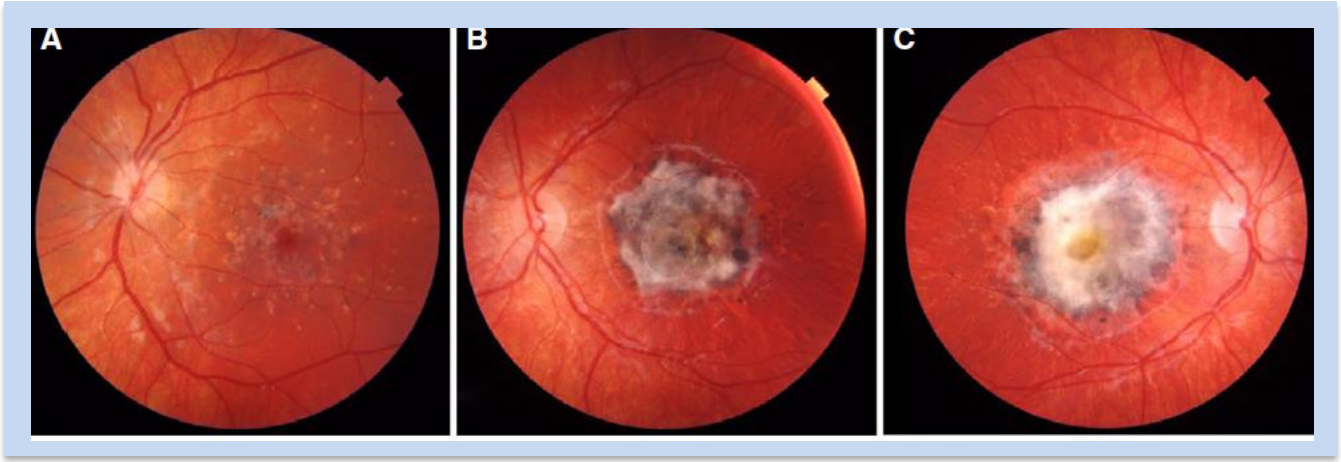


J Child Orthop 2:205–210, 2008



Retinal Changes in PH1 Patients

Oxalate Deposition Varies

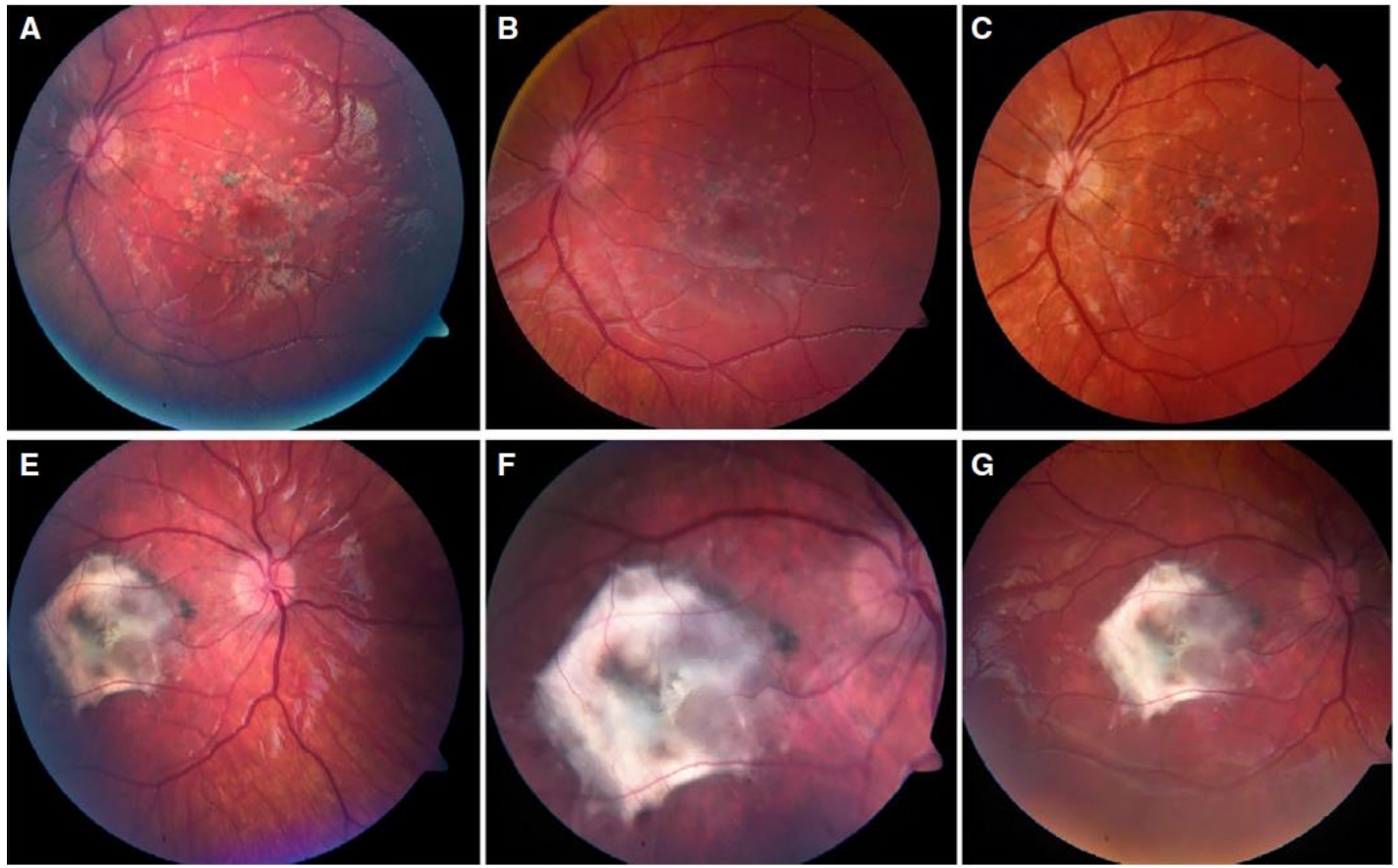


- Oxalate deposition is most related to duration of ESKD and subsequent prolonged period of high plasma oxalate levels
- Retinal changes do not seem to be related to specific PH1 mutations or to any specific higher level of plasma oxalate

Atiskova et al, Am J Transplant 19:3328-3334, 2019

Retinal Changes in PH1 Patients

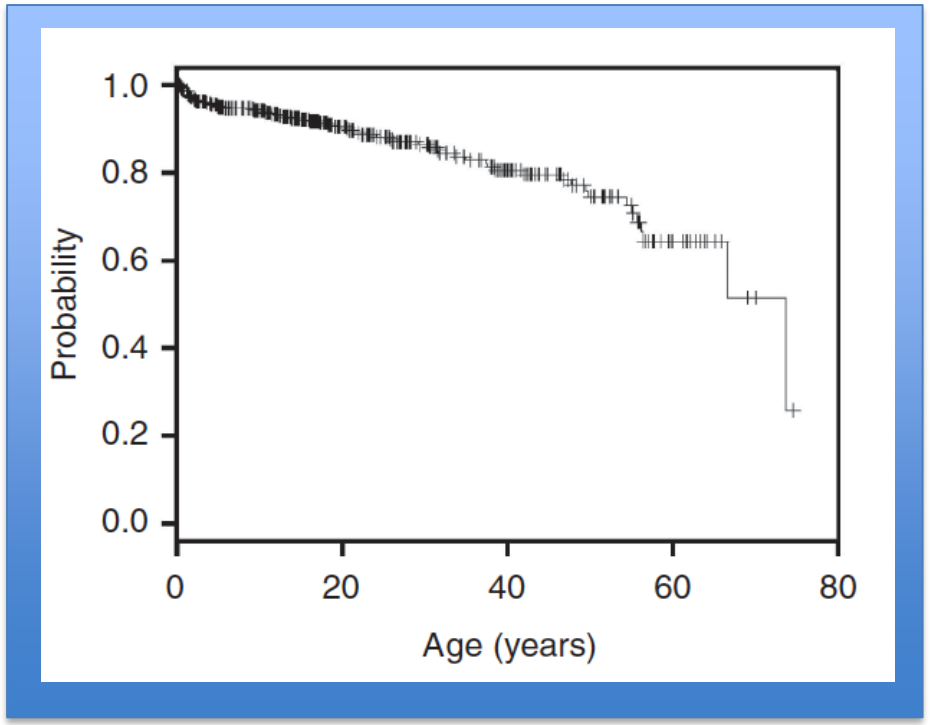
Oxalate Deposition Irreversible

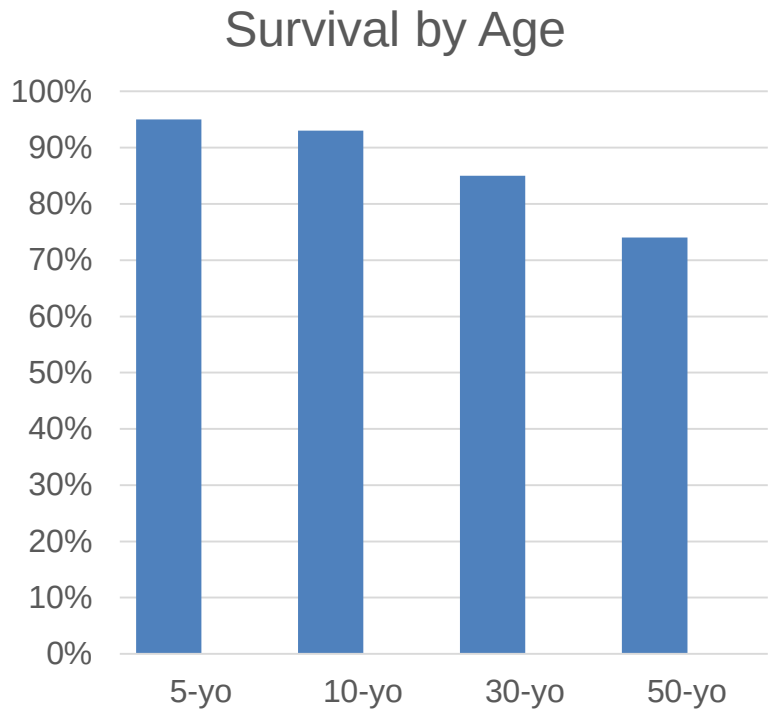


Left eye changes (top row) and right eye changes (bottom row) remain unimproved at 5,7, and 9 years after a successful combined liver-kidney transplant for PH1 with subsequent totally normal plasma oxalate levels

Atiskova et al, Am J Transplant 19:3328-3334, 2019

Survival in PH1 Patients





- Data from OxalEurope PH Consortium
- 67/477 registry patients had died (14%)
- Median age at death 15.5 years old (IQR 2.4-34 yo)
- 96% of deceased patients had reached ESKD at death

Mandrile et al, Kidney Int 86:1197–1204, 2014

Dialysis in PH1 Patients

- Dialysis is usually started for plasma oxlate levels > 30 umol/L regardless of the underlying GFR
- Oxalate production will always exceed clearance by dialysis, even with intensified daily dialysis
- Clearance with hemodialysis dwarves clearance by peritoneal dialysis but its provision is more complex, especially with babies
- There is significant baseline morbidity and mortality on dialysis, but underlying PH1 seems to make these risks greater

Transplantation in PH1 Patients

Kidney vs Liver-Kidney Transplantation

Isolated Kidney Transplant

This could be from living donor or deceased donor

- Considered for those individuals with a pyridoxine-sensitive mutation -- about 30% of those with PH1
- With ongoing pyridoxine therapy post-kidney transplant, there is no risk of recurrent oxalate-mediated nephropathy or the development of systemic oxalosis

Combined Liver Kidney

Usually from deceased donor(s) but living donation has occurred

- Timing of liver transplant can vary – before or with ESKD
- Risk of liver transplant > risk of kidney transplant
- In pyridoxine-resistant mutations, liver transplant after native hepatectomy cures the inborn error of metabolism

Transplant in PH1 Patients

Sequential Liver Kidney vs Combined Liver Kidney

Sequential Liver Kidney

Liver transplant done first, potentially months or years before a kidney transplant

- If done prior to ESKD, may slow down progression to ESKD since ongoing oxalate injury abates
- If done with ESKD, allows for mobilization of systemic oxalate on dialysis, protecting subsequent kidney allograft

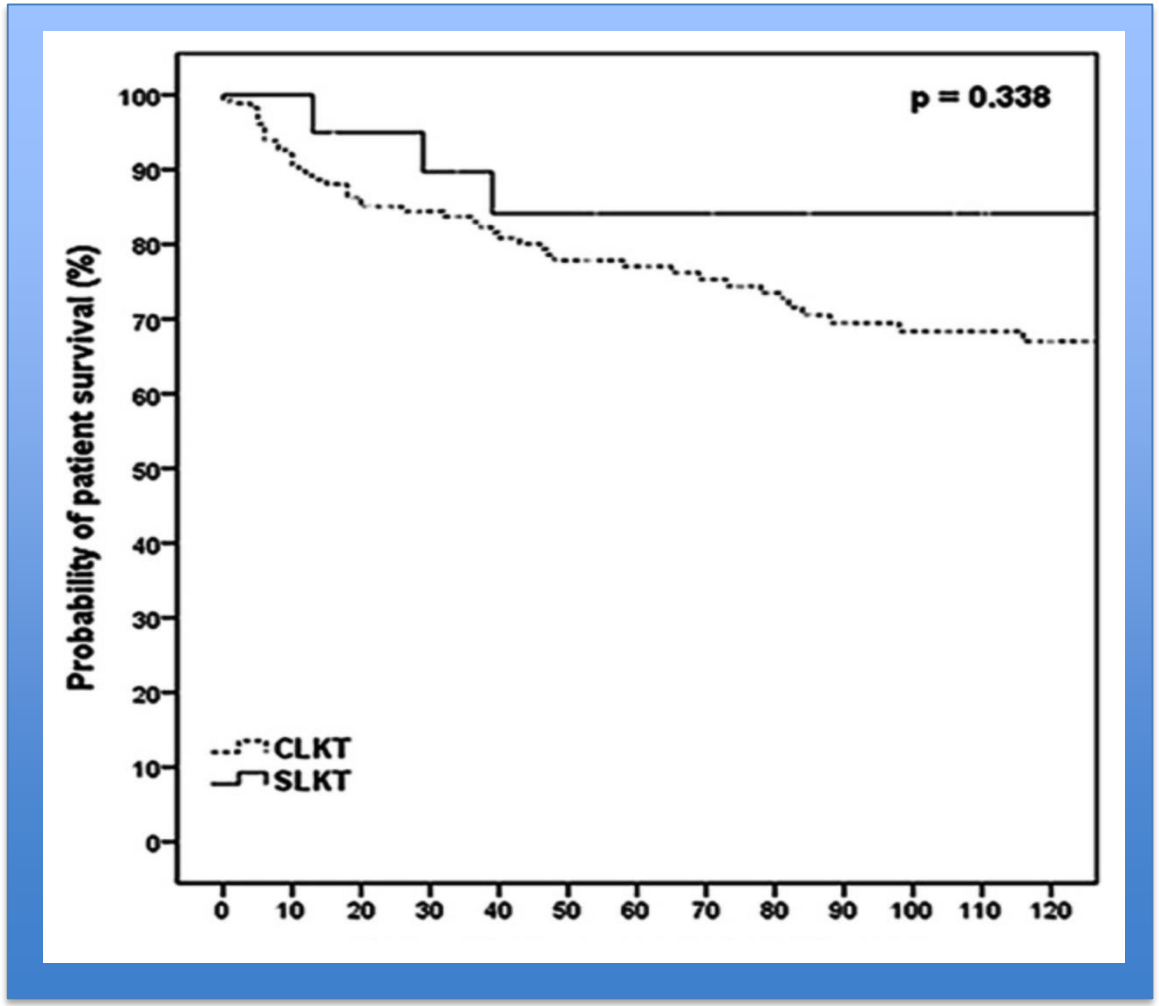
Combined Liver Kidney

Liver and kidney transplants are done together

- Not considered until ESKD
- Allows use of same donor
- Reduces number of transplant surgeries

Liver-Kidney Transplant in PH1 Patients

Patient Survival

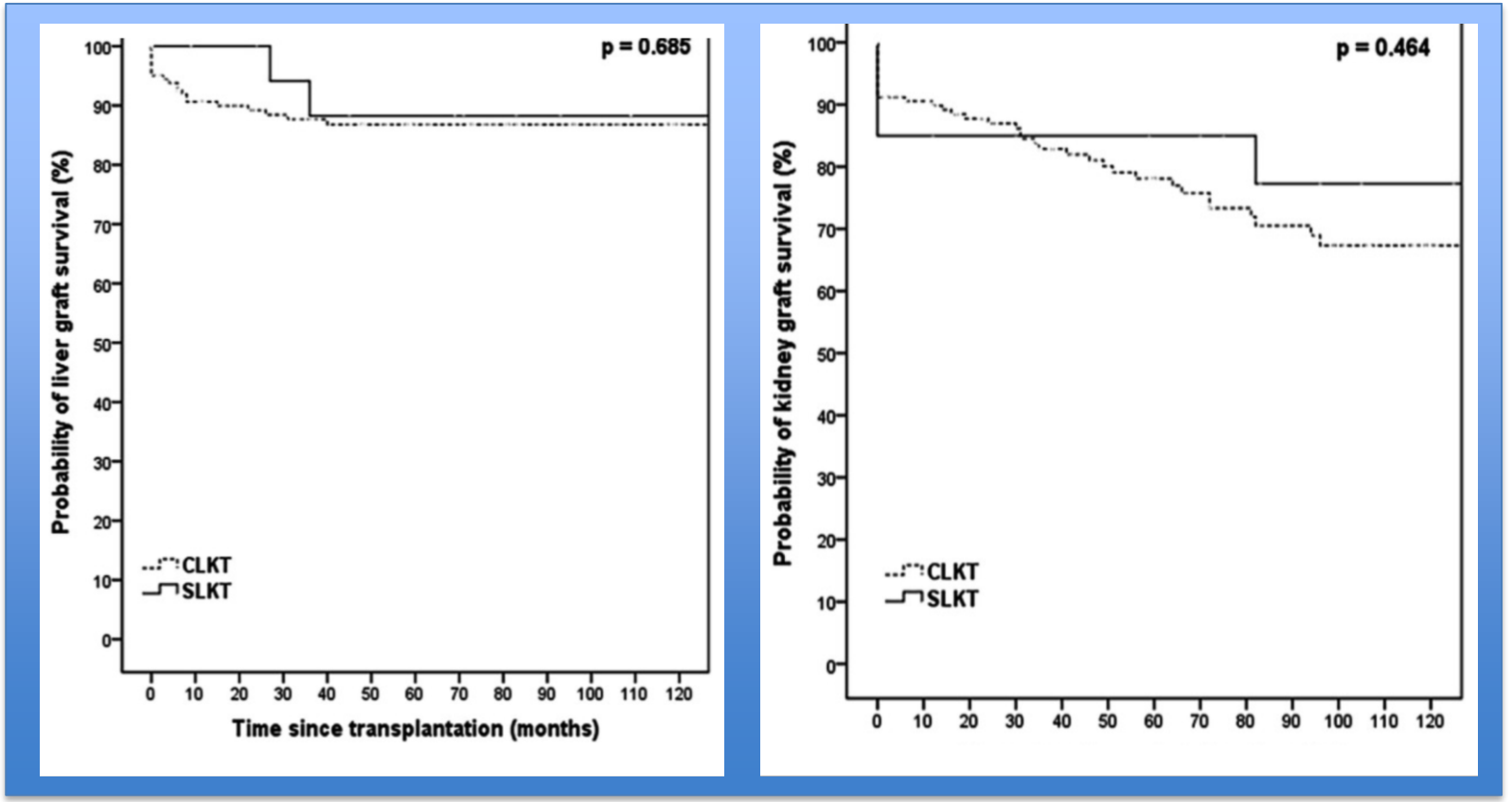


- There is no difference in long-term patient survival comparing SLKT and CLKT
- Patient morbidity over time is significant, with survival at approximately 70%

Xiang et al, BMC Gastroenterol 20:208, 2020

Liver-Kidney Transplant in PH1 Patients

Sequential Liver Kidney vs Combined Liver Kidney Outcomes

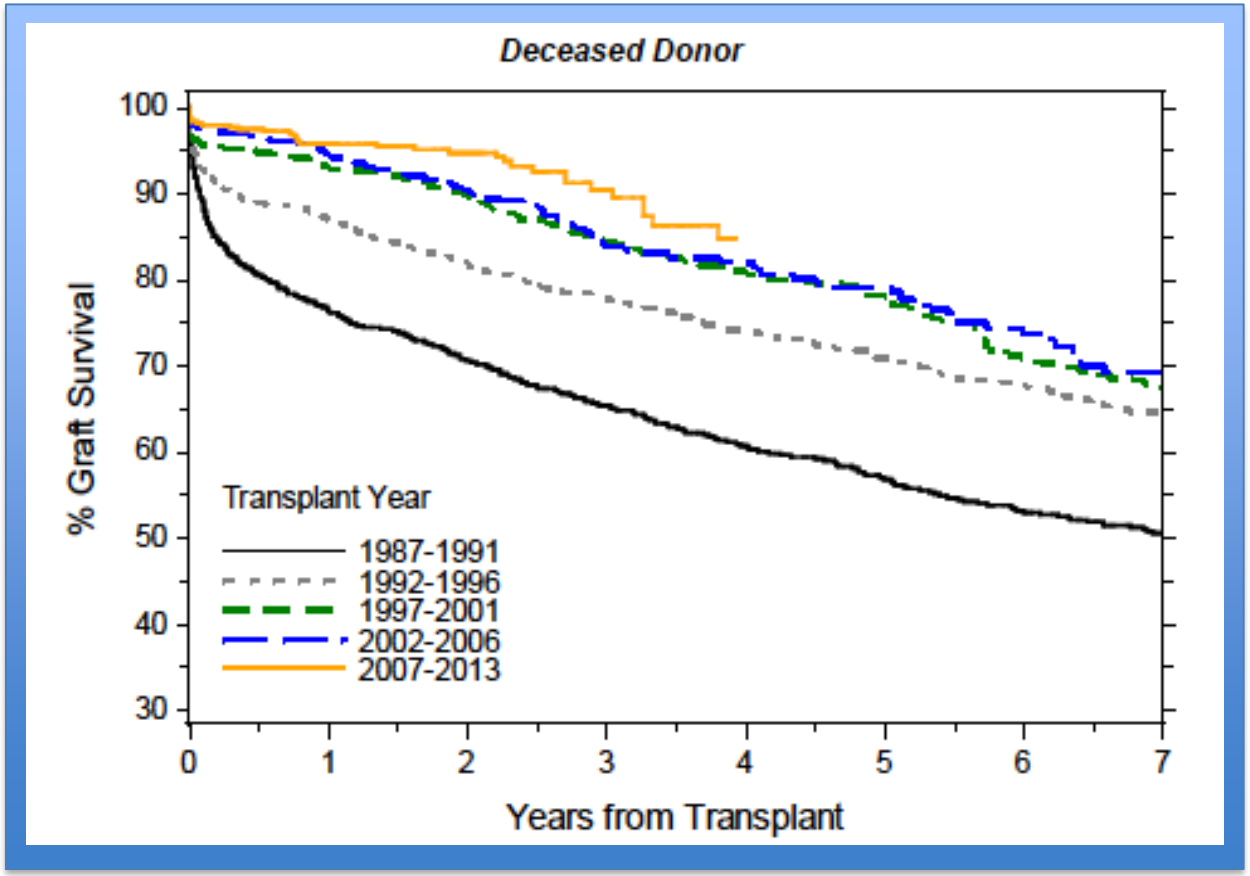


There is no difference in liver or kidney allograft survival between SLKT and CLKT

Mandrile et al, Kidney Int 86:1197–1204, 2014

Transplant in PH1 Patients

Numerous Kidney Allografts May be Necessary



NAPRTCS Transplant Registry

- Largely because of chronic immunologic injury, all renal allografts lose function over time
- Kidneys do not have the regenerative capacity of livers, so renal allografts cannot heal post-transplant injury
- Although dialysis can serve as a bridge to re-transplantation, morbidity and mortality on dialysis is substantially higher than with a renal allograft

Summary

- PH1 is an inherited disorder of oxalate overproduction that frequently leads to kidney failure and to systemic oxalosis with fatal consequences
- PH1 most frequently presents early in life, but there is often a significant lag between presentation and diagnosis
- Clinician ignorance of PH1, its clinical manifestations, and its diagnostic evaluation complicates its diagnosis
- ESKD accelerates PH1 morbidity and mortality
- Liver-kidney transplant is the best current therapy for the majority of PH1 patients with ESKD or systemic oxalosis
- Any successful PH1 therapy must aim at preventing abnormal oxalate synthesis and reducing abnormal oxalate accumulation

Agenda

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

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

Primary Hyperoxaluria Type I Background
- Michael J.G. Somers, M.D. – Associate Chief and Gunnar B. Stickler Chair in Pediatric Nephrology, Division of Nephrology and Medical Director, Renal Dialysis Unit, Boston Children's Hospital; Associate Professor of Pediatrics, Harvard Medical School; President, American Society of Pediatric Nephrology

Phase 1/2 OLE & ILLUMINATE Studies
- Tracy McGregor, M.D. – Sr. Director, Clinical Research

Program Opportunity in PH1
- Pritesh Gandhi, PharmD. – Vice President & General Manager, Lumasiran

Q&A Session

Lumasiran Clinical Development

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 if ≥12 months old
- 6-month dosing

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

COMPLETED ENROLLMENT

EXTENSION PERIOD
Up to 54 months' dosing

ILLUMINATE-C

PH1 patients

Single-arm, open-label n=20
- 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

ENROLLING

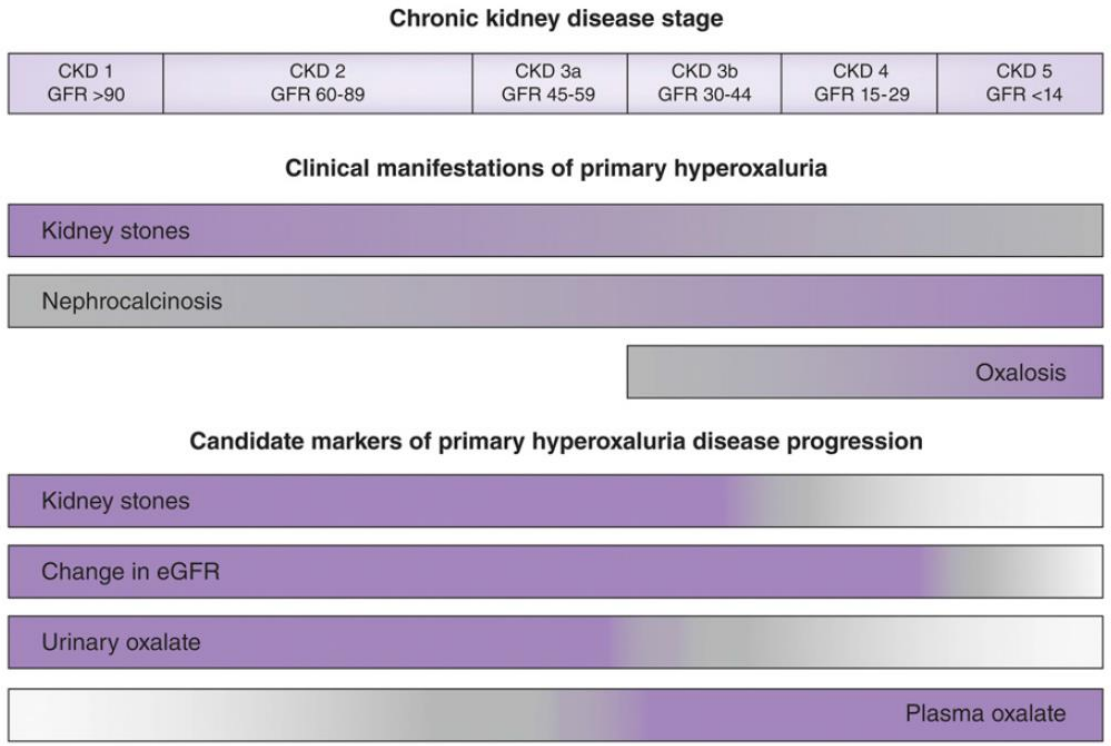
EXTENSION PERIOD
Up to 54 months' dosing

[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

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

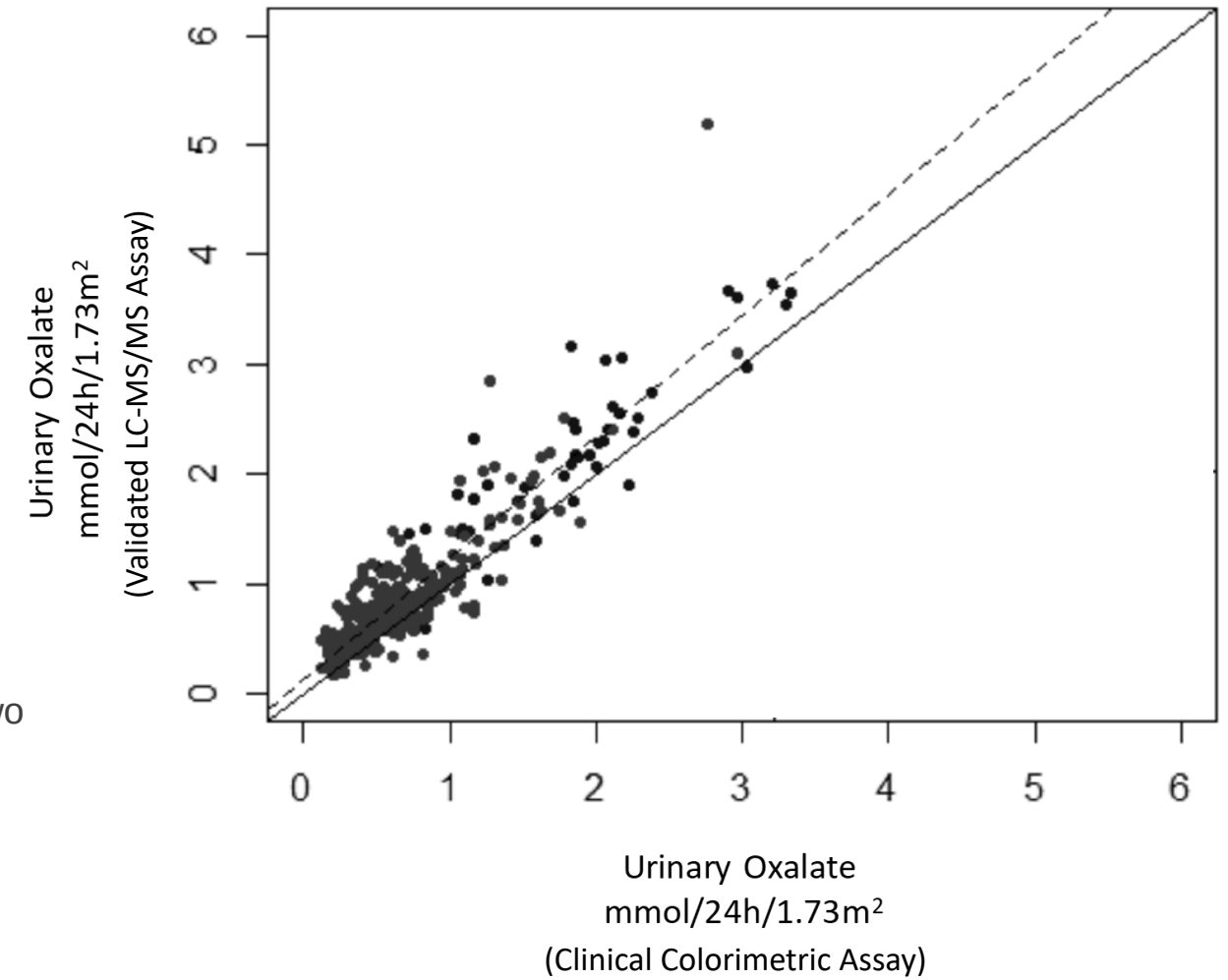


Milliner D, et al. *Clin J Am Soc Nephrol.* 2020; 15(7): 1056-1065.

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

24 hr urinary oxalate corrected for BSA (mmol/24 hr/1.73m^2)
(samples from Phase 1/2 and Phase 2 studies of lumasiran)



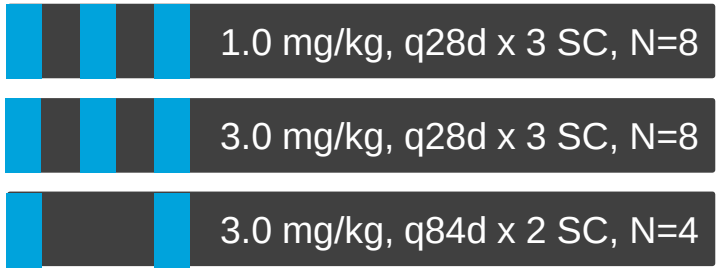
BSA, body surface area; EMA, European Medicines Agency; FDA, US Food and Drug Administration; hr, hour; LC-MS, liquid chromatography-mass spectrometry; MS, mass spectrometry

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 20 patients dosed in Phase 2 OLE, as of Sept 2019
  - Patients have been on study for a median of 10.4 months (range: 7 - 17; N=20)

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



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=20)

- 1.0 mg/kg, q28d SC, N=3
- 3.0 mg/kg, q28d SC, N=7
- 3.0 mg/kg, q84d SC, N=10

- 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

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

Lumasiran Phase 1/2 Study and Open Label Extension

Patient Demographics: Part B (Patients with PH1)

Baseline Characteristics	Result (N=20)
Mean age, years (range)	16 (7 – 44)
Age <18 years	75%
Gender, females	65%
Mean weight, kg (range)	50.0 (21.3 – 112.5)
Mean eGFR, mL/min/1.73m^2 (range)	77 (42 – 131)
Mean Urine Oxalate Content, mmol/24hr/1.73m^2 (range)*	1.69 (0.83 – 2.97)
Mean 24-hour Urine Oxalate:Creatinine Ratio, mg/mg (range)*	0.17 (0.07 – 0.30)
Patients reporting ≥ 1 renal stone in their lifetime	18/20
Patients reporting ≥ 1 renal stone in 12 months prior to enrollment	6/20

eGFR, estimated glomerular filtration rate

*Baseline characteristics are derived from Phase 1/2 study

Lumasiran Phase 2 OLE Study Results

Safety

Continued dosing with lumasiran was generally well tolerated in patients with PH1

- No discontinuations from study treatment
- A single patient (1/20; 5.0%) reported 2 SAEs (traumatic brain injury and bone contusion sustained during car accident); none assessed as related to study drug
- AEs reported in 19/20 (95%) of patients; majority were reported in single patients
  - Majority of AEs were mild in severity and assessed as unrelated to study drug
  - AEs reported in more than 1 patient were: injection site reaction (n=4); headache, oropharyngeal pain (n=3); gastroenteritis, viral gastroenteritis, pyrexia, vomiting (n=2)
  - 4/20 (20%) patients reported injection site reactions; all were mild and assessed as related to study drug
  - No AEs of renal stones reported
- No clinically significant laboratory changes

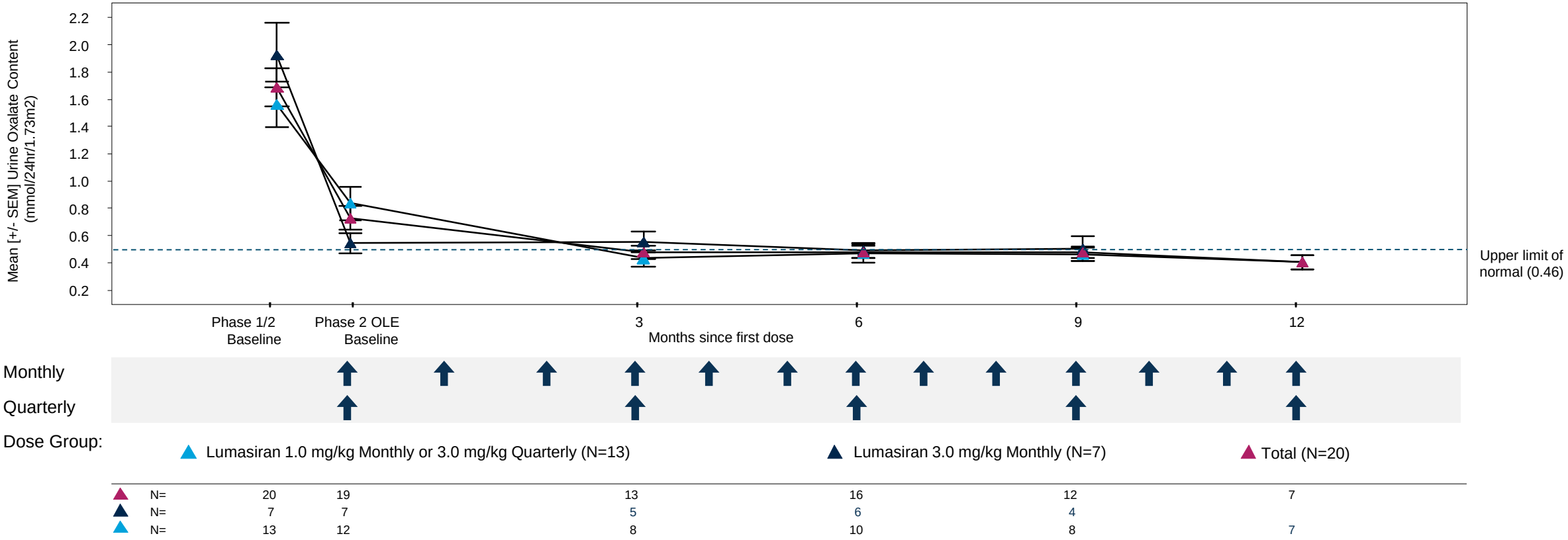
T. McGregor, presented at the ASN 2019 Annual Meeting, Washington D.C., 09 November 2019
Data cut-off: 19 Sep 2019; SAE, serious adverse event

Lumasiran Phase 2 OLE Study Results

Pharmacodynamics: Urinary Oxalate Content in 24-hour Urinary Collections†

Mean maximal reduction in urinary oxalate content of 76% (range: 43 – 91%) relative to Phase 1/2 baseline in all cohorts (N=19)‡

- 100% of patients achieved a urinary oxalate level <1.5x ULN and 68% of patients achieved a urinary oxalate level within normal range (N=19)^



T. McGregor, presented at the ASN 2019 Annual Meeting, Washington D.C., 09 November 2019

Data cut-off: 12 Sep 2019; †Only data points with at least 3 contributing patients are represented

‡Patients who had a valid 24-hour urinary oxalate assessment; ^1.5x ULN is defined as 0.69 mmoL/24hr/1.73m2

Lumasiran Phase 1/2 and Phase 2 OLE Renal Stones

Post-hoc analysis conducted based on data collected for renal stone adverse events‡

	Patients Reporting ≥ 1 Renal Stone	Total Number of Renal Stones	Duration of Follow-Up
Historical (Prior 12 Months)^	6/20	9	20 patient-years
Phase 1/2 Part B	4/20	7	7.8 patient-years*
Phase 2 OLE	0/20	0	18.7 patient-years†

^Patients reported number of renal stones in the 12 months prior to enrollment in the Phase 1/2 Study

*From first dose to last dose + 84 days

†From first dose to data cut-off: 19 Sep 2019. Interval between Phase 1/2 Part B and Phase 2 OLE not represented in these data.

‡.Renal stones not collected as an efficacy endpoint; any renal stone meeting adverse event (AE) definition is reported and recorded as an AE. Renal stones were identified in AE listings by medical review

Lumasiran ILLUMINATE•A Phase 3 Study

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

Patient Population (N=39)

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

2:1 RANDOMIZATION

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

or

Placebo
qM x 3 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)

Extension Phase

ILLUMINATE•A

Lumasiran has received FDA Breakthrough and EMA PRIME Designations

Full Results Presented June 2020

NDA under Priority Review, MAA under Accelerated Review

PDUFA Action Date of December 3rd, 2020

*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

ILLUMINATE-A: Baseline Clinical Characteristics

Balanced Between Placebo and Lumasiran Groups

Clinical characteristic	Placebo (N=13)	Lumasiran (N=26)	Overall (N=39)
Mean 24 hr urinary oxalate excretion corrected for BSA[a] (SD), mmol/24 hr/1.73 m²	1.79 ± 0.68	1.84 ± 0.60	1.82 ± 0.62
Mean 24 hr urinary oxalate:creatinine ratio[b] (SD), mmol/mmol	0.237 ± 0.110	0.209 ± 0.101	0.218 ± 0.104
Mean plasma oxalate[c] (SD), µmol/liter	15.5 ± 7.3	14.8 ± 7.6	15.0 ± 7.4
eGFR, mL/min/1.73 m²			
Overall, mean (SD)	78.9 ± 26.8	83.0 ± 25.5	81.6 ± 25.7
≥90 (CKD stage 1), n (%)	4 (30.8)	9 (34.6)	13 (33.3)
60–<90 (CKD stage 2), n (%)	6 (46.2)	13 (50.0)	19 (48.7)
45–<60 (CKD stage 3a), n (%)	1 (7.7)	2 (7.7)	3 (7.7)
30–<45 (CKD stage 3b), n (%)	2 (15.4)	2 (7.7)	4 (10.3)
Pyridoxine (vitamin B6) use, n (%)	9 (69.2)	13 (50.0)	22 (56.4)
Nephrocalcinosis grade ≥1, n (%)[d]	12 (92.3)	17 (70.8)	29 (78.4)
Number of patients with reported history of symptomatic renal stone events[e], n (%)			
Lifetime	10 (76.9)	23 (88.5)	33 (84.6)
12 months prior to consent	4 (30.8)	11 (42.3)	15 (38.5)

[a] ULN is 0.514 mmol/24 hr/1.73 m². [b] ULN is 0.0799 mmol/mmol. [c] ULN is 12.11 µmol/liter. [d] Denominator includes all patients who had a graded renal ultrasound at baseline. [e] A renal stone event is defined as an event that includes at least one of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, or macroscopic hematuria due to a renal stone

BSA, body surface area; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; hr, hour; SD, standard deviation; ULN, upper limit of normal

ILLUMINATE-A: Lumasiran Safety Profile

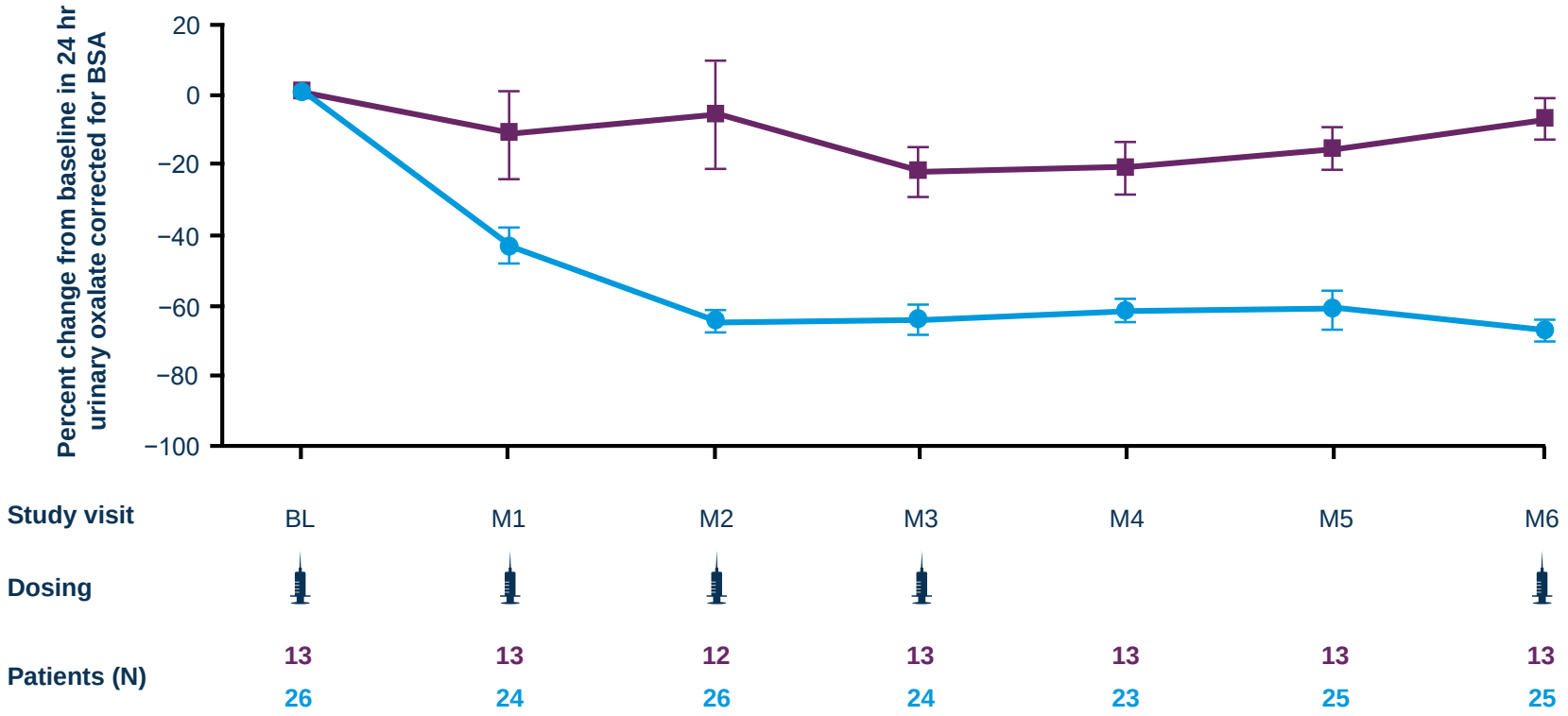
- There were no deaths, severe, or serious AEs
- All AEs were mild or moderate in severity
- Most common related AEs were injection-site reactions
  - All were transient and mild in severity, with no treatment interruption or discontinuation
  - Most common symptoms were erythema, pain, pruritus, or discomfort at the injection site
- No hepatic AEs reported in either group
- No clinically relevant changes in laboratory measures, vital signs, or electrocardiograms related to lumasiran were observed

Event, n (%)	Placebo (N=13)	Lumasiran (N=26)
AEs	9 (69)	22 (85)
AEs occurring in ≥10% of patients in either group		
Injection-site reactions[a]	0	9 (35)
Headache	3 (23)	3 (12)
Rhinitis	2 (15)	2 (8)
Upper respiratory infection	2 (15)	2 (8)
AE leading to discontinuation of study treatment[b]	0	1 (4)
AE leading to study withdrawal	0	0
Death	0	0
Serious AE	0	0
Severe AE	0	0

[a] Includes injection-site reactions, injection-site erythema, and injection-site pain. [b] Fatigue and disturbance in attention
AE, adverse event

ILLUMINATE-A Primary Endpoint: Percent Change in 24 hr Urinary Oxalate from Baseline to Month 6

Rapid and Sustained Reduction in 24 hr Urinary Oxalate Levels



LS mean average of M3–M6	
−11.8%	Placebo (N=13)
−65.4%	Lumasiran (N=26)

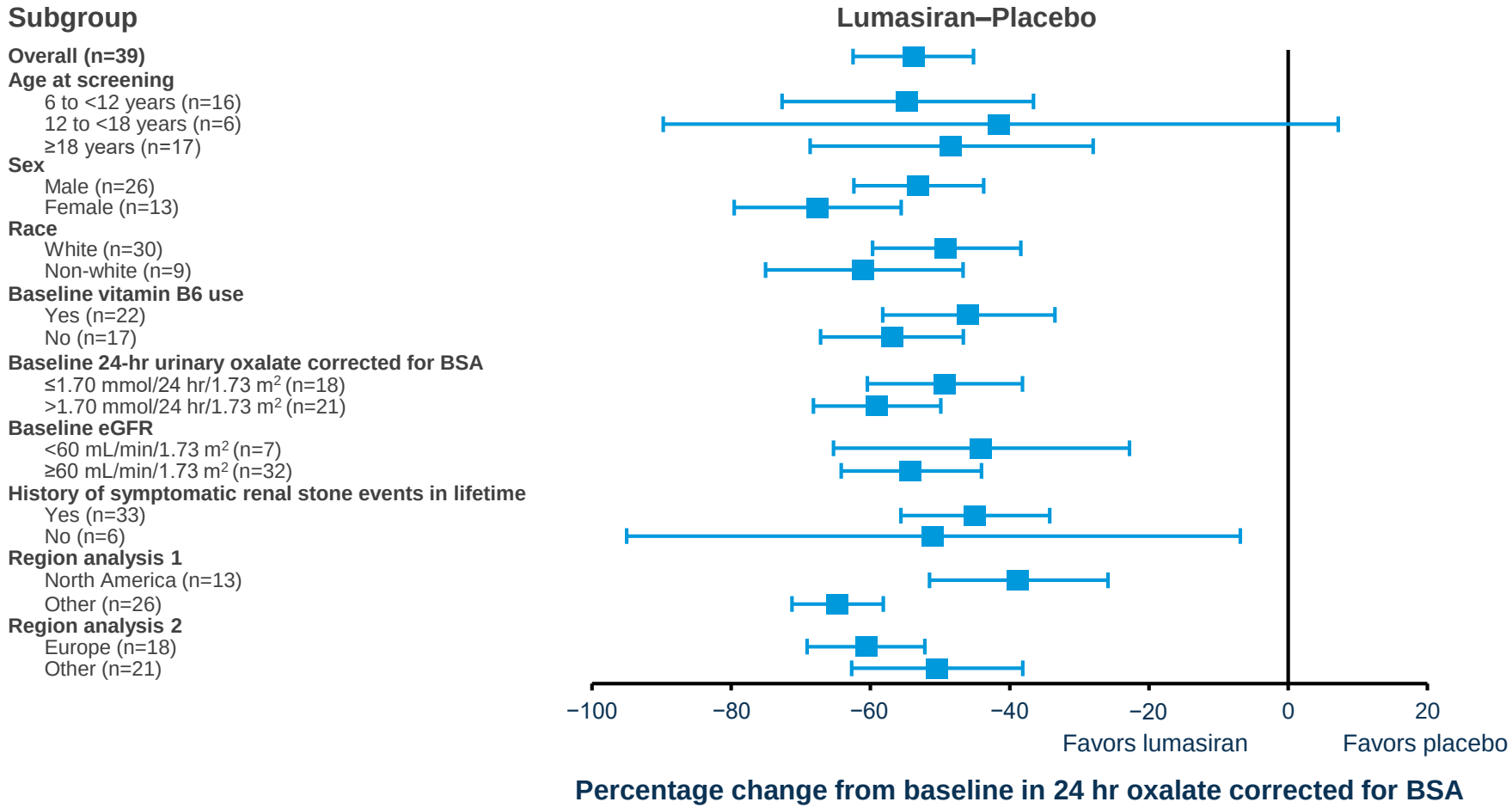
Difference in LS mean average M3–M6 (Lumasiran−Placebo): −53.5%; p-value: 1.7×10^{-14}

Mean maximal reduction: 76.0%

Data in graph are mean ± SEM of observed values; The Month 6 dose defines the beginning of the 54 month extension period
BL, baseline; BSA, body surface area; hr, hour; LS, least squares; M, month; SEM, standard error of the mean

ILLUMINATE-A Subgroup Analysis: Percent Change in 24 hr Urinary Oxalate from Baseline to Month 6

Consistent Treatment Effect Across All Subgroups, Including Baseline 24 hr Urinary Oxalate Excretion, Pyridoxine Use, and eGFR



Subgroup analysis was performed with a restricted maximum likelihood-based MMRM model and a forest plot was generated, showing the associated 95% CI of the treatment effect in urinary oxalate corrected for BSA

BSA, body surface area; CI, confidence interval; eGFR, estimated glomerular filtration rate; hr, hour; MMRM, mixed-effect model repeated measures

ILLUMINATE-A: Secondary Endpoints

All Tested Secondary Endpoints Achieved Statistical Significance

Secondary Endpoints	Placebo (N=13)	Lumasiran (N=26)	Difference, Lumasiran−Placebo	p-value
Absolute change in 24 hr urinary oxalate corrected for BSA from baseline to month 6[a] (95% CI), mmol/24 hr/1.73 m^2	–0.27 (–0.44 to –0.10)	–1.24 (–1.37 to –1.12)	–0.98 (–1.18 to –0.77)	**1.2×10^{-11}**
Percent change in 24 hr urinary oxalate:creatinine ratio from baseline to month 6[a] (95% CI)	–10.8 (–21.6 to 0.0)	–62.5 (–70.7 to –54.4)	–51.8 (–64.3 to –39.3)	**5.0×10^{-10}**
Percent change in plasma oxalate from baseline to month 6[a,b] (95% CI)	–0.3 (–9.1 to 8.5)	–39.8 (–45.8 to –33.8)	–39.5 (–50.1 to –28.9)	**2.9×10^{-8}**
Proportion of patients with 24 hr urinary oxalate level at or below 1.5 × ULN at month 6[c] (95% CI)	0.00 (0.00 to 0.25)	0.84 (0.64 to 0.95)	0.84 (0.55 to 0.94)[d]	**8.3×10^{-7}**
Proportion of patients with 24 hr urinary oxalate level at or below ULN at month 6[c] (95% CI)	0.00 (0.00 to 0.25)	0.52 (0.31 to 0.72)	0.52 (0.23 to 0.70)[d]	**0.0010**
Absolute change in plasma oxalate from baseline to month 6[a,b] (95% CI), µmol/liter	1.3 (–1.0 to 3.5)	–7.5 (–9.0 to –5.9)	–8.7 (–11.5 to–6.0)	**3.9×10^{-7}**
Change in eGFR from baseline to month 6 (SD), mL/min/1.73 m^2	–0.1 (6.5)	–2.6 (10.6)	Not applicable[d]	Not applicable[d]

[a]Estimated by MMRM. [b]Based on the plasma oxalate analysis set, including patients who had a baseline plasma oxalate level ≥1.5 × LLOQ. [c]Analyzed using a Cochran–Mantel–Haenszel test.
[d]As prespecified, no statistical testing was performed
BSA, body surface area; CI, confidence interval; eGFR, estimated glomerular filtration rate; hr, hour; LLOQ, lower limit of quantification; MMRM, mixed-effect model repeated measures; SD, standard deviation; ULN, upper limit of normal

ILLUMINATE-A Exploratory Endpoints: Renal Stone Events and Nephrocalcinosis

No Apparent Difference Between Treatment Groups with Regard to Renal Stone Events; 3 Patients in Lumasiran Treatment Group with Improvements in Nephrocalcinosis

Renal stone events[a]

	Placebo (N=13)	Lumasiran (N=26)
BASELINE		
Number of patients with reported history of symptomatic renal stone events, n (%) Lifetime 12 months prior to consent	10 (76.9) 4 (30.8)	23 (88.5) 11 (42.3)
TREATMENT PERIOD		
Number of patients with post-baseline renal stone events, n (%)	2 (15.4)	5 (19.2)

Nephrocalcinosis[b]

Change from baseline to month 6	Placebo (N=12)	Lumasiran (N=22)
Unilateral improvement (1 grade)	0	2
Bilateral improvement (≥1 grade)	0	1
Unilateral worsening (1 grade)	1	0
No change	11	19

[a] A renal stone event was defined as an event that includes at least one of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, or macroscopic hematuria due to a renal stone

[b] In the subset of patients with renal ultrasounds at baseline and month 6

Lumasiran ILLUMINATE•B Phase 3 Study

Open-Label Study in Pediatric Primary Hyperoxaluria Type 1 Patients

Patient Population (N=18)

- Infants and children <6 years
- Elevated urinary oxalate:creatinine ratio
- Confirmed alanine glyoxylate aminotransferase (*AGXT*) mutation
- eGFR >45 mL/min/1.73 m^2 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 from baseline through Month 6* in 24-hour urinary oxalate corrected for body surface area

▶ **Open-Label Extension ‡**

ILLUMINATE•B

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; *average of 24h UOx of months 3-6

Lumasiran ILLUMINATE•C Phase 3 Study

Open-Label Study in Primary Hyperoxaluria Type I Patients with Impaired Renal Function

NOW ENROLLING

Patient Population (N=20)

- All ages
- Plasma oxalate ≥20 µmol/L
- Confirmed alanine glyoxylate aminotransferase (*AGXT*) mutation
- eGFR ≤45 mL/min/1.73 m^2 if ≥12 months old; elevated serum creatinine if <12 months old

Open-Label

Lumasiran
(Cohort A – No hemodialysis)

Three monthly loading doses then maintenance dosing dependent on weight†

Lumasiran
(Cohort B – Hemodialysis)

Three monthly loading doses then maintenance dosing dependent on weight†

Primary Endpoint

- Percent change in plasma oxalate from baseline (cohort A) or predialysis plasma oxalate (cohort B) to 6 months

Open-Label Extension

ILLUMINATE•C

Topline ILLUMINATE-C results expected **2021**

NCT04152200; EudraCT Number: 2019-001346-17

†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

Agenda

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

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

Primary Hyperoxaluria Type I Background
- Michael J.G. Somers, M.D. – Associate Chief and Gunnar B. Stickler Chair in Pediatric Nephrology, Division of Nephrology and Medical Director, Renal Dialysis Unit, Boston Children's Hospital; Associate Professor of Pediatrics, Harvard Medical School; President, American Society of Pediatric Nephrology

Phase 1/2 OLE & ILLUMINATE Studies
- Tracy McGregor, M.D. – Sr. Director, Clinical Research

Program Opportunity in PH1
- Pritesh Gandhi, PharmD. – Vice President & General Manager, Lumasiran

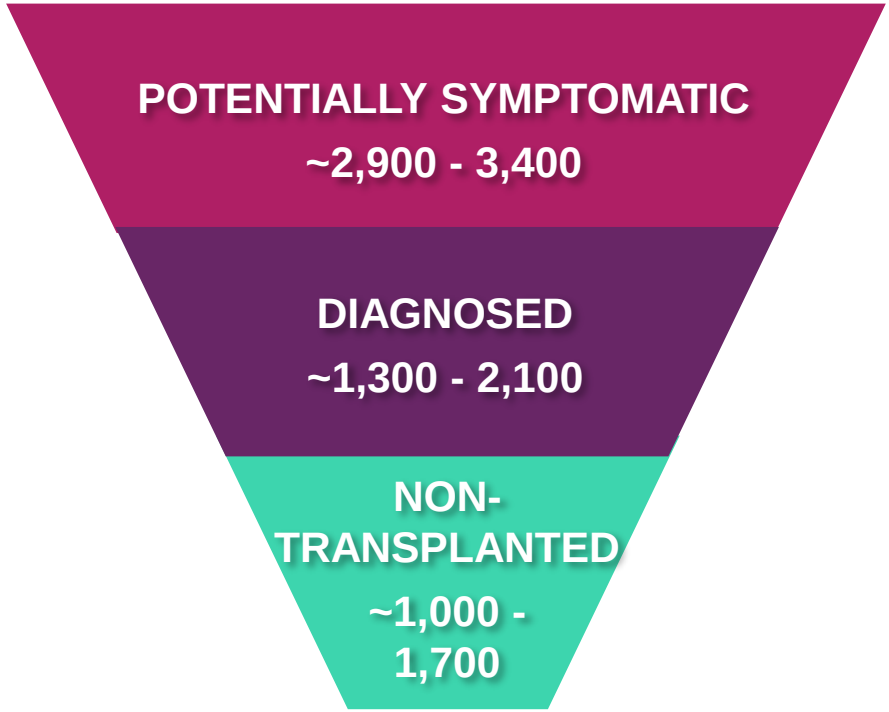
Q&A Session

Lumasiran Market Opportunity

Estimated U.S./EU Prevalence and Addressable Population*

MUTATION PREVALENCE[1]	POTENTIALLY SYMPTOMATIC PREVALENCE^	DIAGNOSED PREVALENCE[2-4]	DIAGNOSED & NON-TRANSPLANTED[5]
~4.3 per Million (U.S./EU)	~3.5 to 4.0 per Million (U.S./EU)	~1.5 to 2.5 per Million (U.S./EU)	~1.2 to 2.0 per Million (U.S./EU)

Patients in the U.S. / EU†



Opportunity for growth with increased awareness and diagnosis, as well as global commercial expansion

*Assumed indication for the treatment of PH1 pediatric and adult patients, regardless of stage of disease

†US population=328MM, EU population (including UK) = 513MM

^includes patients that are presymptomatic, subclinical, or symptomatic

Sources: 1. Hopp K, et al. *J Am Soc Nephrol.* 2015 Feb 2; **2.** Cochat et al. *Nephrol Dial Transplant.* 1995; 10: 3–7; **3.** Kopp and Leumann. *Nephrol Dial Transplant*. 1995; 10: 2224–2227; **4.** van Woerden, et al. *Nephrol Dial Transplant*. 2003; 18: 273–279; **5.** Data on file. Anlylam chart review studies (US and EU) estimated 17% transplant rate, rounded up to 20%; **6.** Cochat P, et al. *N Engl J Med.* 2013 Nov 28;369(22):2163; **7.** Harambat J. *Clin J Am Soc Nephrol*. 2012 Mar;7(3):458-65; **8.** Kamoun A. *Pediatr Nephrol.* 1996 Aug;10(4):479-82.

Lumasiran Market Opportunity

First-in-Class Target Product Profile in Ultra-Rare Orphan Disease

PREVALENCE	DIAGNOSIS	DISEASE BURDEN	COST BURDEN
~2,900 – 3,400	**~50%**	**30–65%**	**$1M+**
potentially symptomatic patients in U.S./EU	currently diagnosed[1]; mean time to diagnosis ~6 years[2]	reach end-stage renal disease before diagnosis[3]	average cost (transplant & lifelong immunosuppression)

LUMASIRAN | PRIMARY HYPEROXALURIA TYPE 1

>$500M potential market opportunity

[1] Hopp R, et al. J Am Soc Nephrol. 2015;26:2559-2570
[2] Harambat J, et al. Kidney Int. 2010;77(5):443-449

Increasing PH1 Awareness

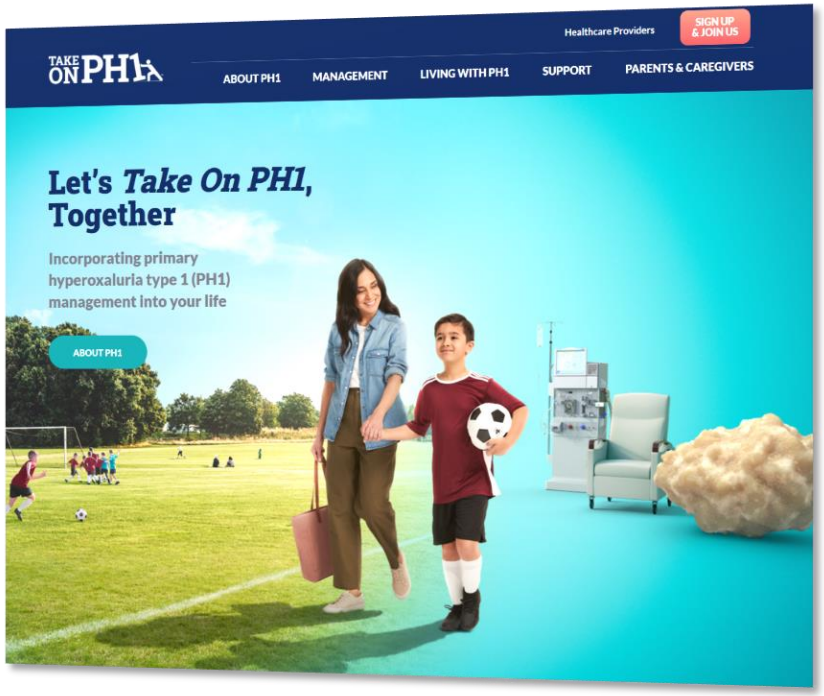
Education Initiatives Developed for Physicians and Patients

Behind the Stone

aboutph1.com

PH1 of a Kind

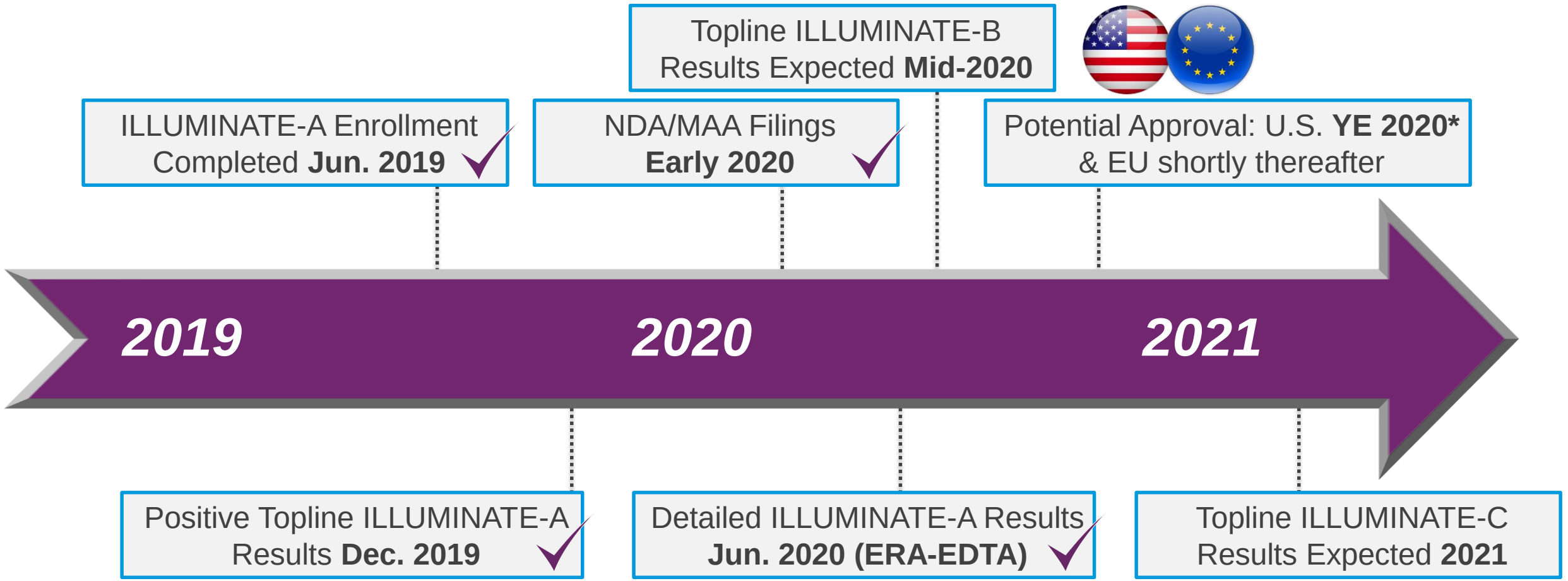
ph1ofakind.com



Take on PH1

takeonph1.com

Next Steps for Lumasiran



* PDUFA action date 12/03/2020

Agenda

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

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

Primary Hyperoxaluria Type I Background
- Michael J.G. Somers, M.D. – Associate Chief and Gunnar B. Stickler Chair in Pediatric Nephrology, Division of Nephrology and Medical Director, Renal Dialysis Unit, Boston Children's Hospital; Associate Professor of Pediatrics, Harvard Medical School; President, American Society of Pediatric Nephrology

Phase 1/2 OLE & ILLUMINATE Studies
- Tracy McGregor, M.D. – Sr. Director, Clinical Research

Program Opportunity in PH1
- Pritesh Gandhi, PharmD. – Vice President & General Manager, Lumasiran

Q&A Session

Upcoming RNAi Roundtables

Patisiran and Vutrisiran, in Development for the Treatment of ATTR Amyloidosis

- Thursday, September 3, 11:00 am ET

Givosiran, for the Treatment of Acute Hepatic Porphyria

- Monday, September 14

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