Lumasiran, for the Treatment of Primary Hyperoxaluria Type 1

August 19, 2021

RNAi ROUNDTABLE 2021

Alnylam PHARMACEUTICALS

Agenda

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

Introduction
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Primary Hyperoxaluria Type 1 Burden of Disease and Diagnosis
- Jeffrey M. Saland, MD, MSCR – Professor, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Recent Highlights, Lumasiran Program: Primary Hyperoxaluria Type 1 & Recurrent Stone Formers
- John Gansner, MD, PhD – Director, Clinical Research

Lumasiran Commercial Progress PH1
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, 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, including expectations regarding our aspiration to become a leading biotech company, and the planned achievement of our "*Alnylam P^{5}x25*" strategy, plans for additional global regulatory filings and the continuing product launches of our approved products and the approved product of our partner, plans for continued development, regulatory review and expected regulatory filings for vutrisiran and, by our partner, for fitusiran, the timeline for continued development and results from ongoing and planned clinical studies of lumasiran and plans for potential supplemental regulatory filings, the potential of OXLUMO (lumasiran) as a treatment option for patients with PH1, estimates of the PH1 patient population, plans for additional global regulatory filings and the continuing launch of OXLUMO in additional territories to drive growth, and the potential of global, multi-channel initiatives underway to improve PH1 disease awareness. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including lumasiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products, including OXLUMO, globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO (and potentially vutrisiran) in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines 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 – Senior Director, Investor Relations & Corporate Communications

Introduction
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Primary Hyperoxaluria Type 1 Burden of Disease and Diagnosis
- Jeffrey M. Saland, MD, MSCR – Professor, Icahn School of Medicine at Mount Sinai, New York, NY, USA

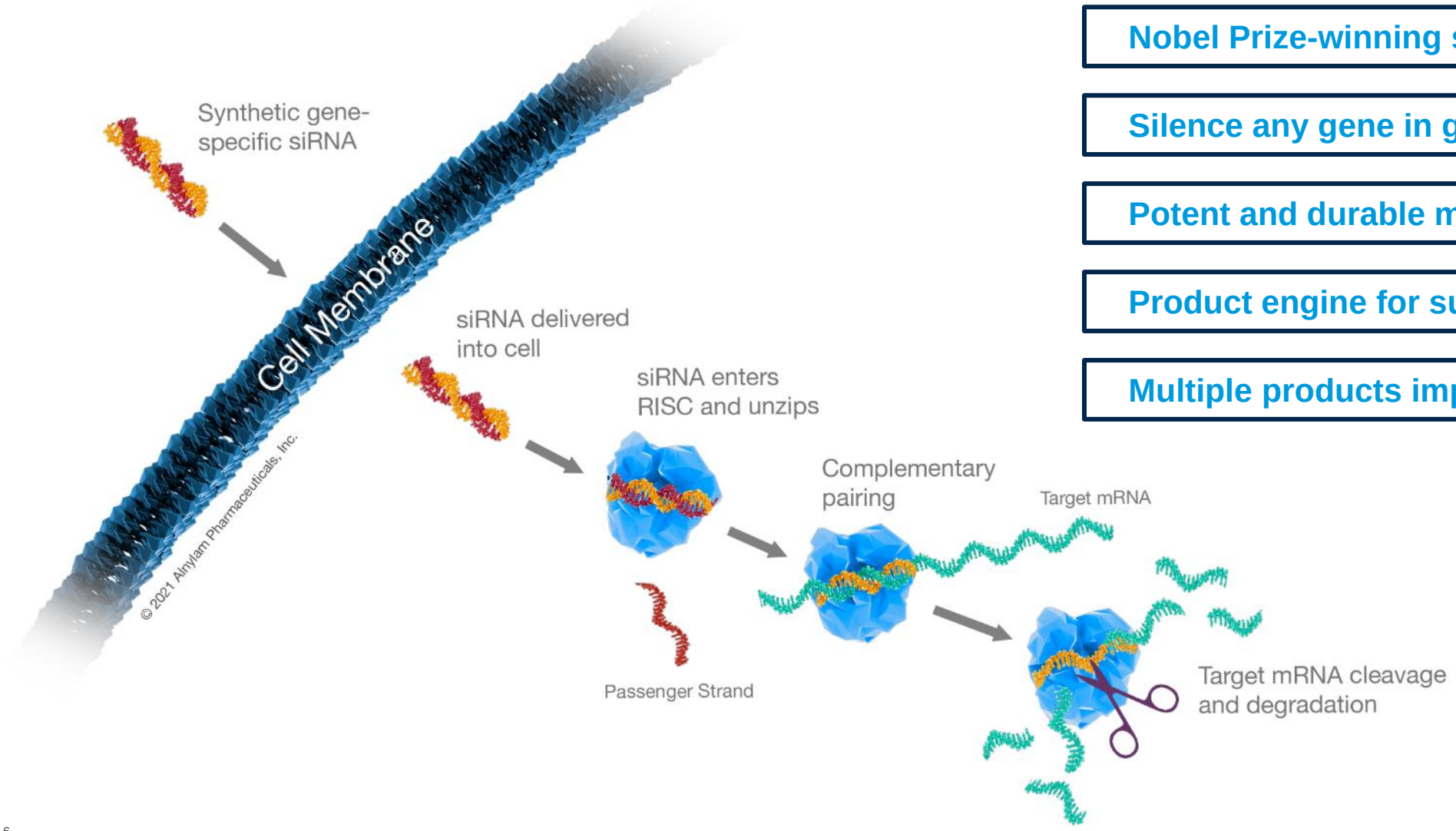
Recent Highlights, Lumasiran Program: Primary Hyperoxaluria Type 1 & Recurrent Stone Formers
- John Gansner, MD, PhD – Director, Clinical Research

Lumasiran Commercial Progress PH1
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Q&A Session

RNAi Therapeutics: New Class of Innovative Medicines

Clinically and Commercially Established Approach with Transformational Potential



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

Alnylam P5x25

Patients: Over 0.5 million on Alnylam RNAi therapeutics globally

Products: 6+ marketed products in rare and prevalent diseases

Pipeline: Over 20 clinical programs, with 10+ in late stages and 4+ INDs per year

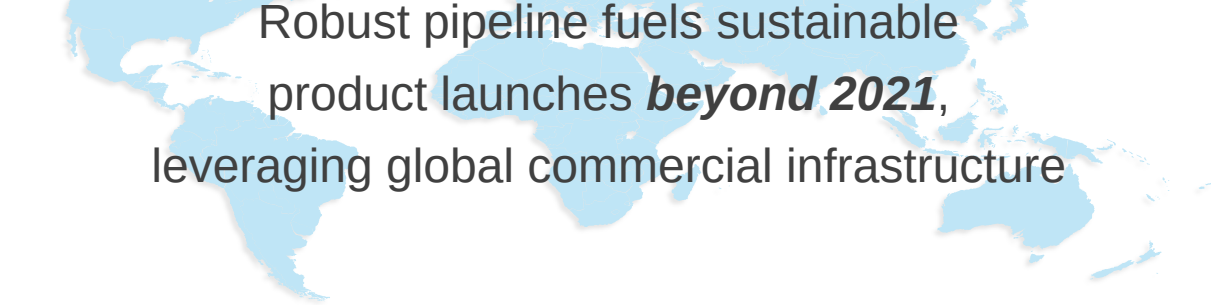
Performance: ≥40% revenue CAGR through YE 2025

Profitability: Achieve sustainable non-GAAP profitability within period

Additional Alnylam and Partner Launches Planned Over Next 12-24 Months

Compelling Commercial Profile of Existing and Emerging Medicines

2018	2019	2020	2020	2022-2023	
onpattro® (patisiran) lipid complex injection 10 mg/5 mL	GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL	OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL	**Leqvio®** (inclisiran)	**Vutrisiran**	**Fitusiran***
ONPATTRO is indicated in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults[1]	GIVLAARI is indicated in the U.S. for the treatment of adults with acute hepatic porphyria[2]	OXLUMO is indicated in the U.S. for the treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels in pediatric and adult patients[3]	Leqvio is approved in the EU for the treatment of adults with hypercholesterolemia or mixed dyslipidemia[4] *NDA resubmitted* *PDUFA date January 1, 2022*	ATTR amyloidosis *Positive HELIOS-A Phase 3 results* *PDUFA date April 14, 2022*	Hemophilia *Phase 3 ATLAS data expected early 2022*



Robust pipeline fuels sustainable product launches ***beyond 2021***, leveraging global commercial infrastructure

[1] ONPATTRO is approved in U.S. and Canada for the PN of hATTR amyloidosis in adults, and in EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. For additional information on ONPATTRO, see Full Prescribing Information

[2] GIVLAARI is approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older. For additional information on GIVLAARI, see Full Prescribing Information

[3] OXLUMO is approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups. For additional information on OXLUMO, see Full Prescribing Information

[4] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran under a license and collaboration agreement with Alnylam Pharmaceuticals, a leader in RNAi therapeutics

* Sanofi Genzyme is leading and funding development of fitusiran and will commercialize fitusiran, if successful

Anticipated dates of launch based on current development timelines for investigational therapeutics and assuming positive pivotal study data and regulatory approval

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

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

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis-PN*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Vutrisiran*	*hATTR Amyloidosis-PN*			●	Global
Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran*	*ATTR Amyloidosis*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Kidney Stones*	●	●		Global
Cemdisiran*	*Complement-Mediated Diseases*	●			50-50
Cemdisiran/Pozelimab Combo[6]*	*Complement-Mediated Diseases*	●			Milestone/Royalty
Belcesiran[7]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[8]*	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT)*	*Hypertension*	●			Global
ALN-HSD*	*NASH*	●			50-50

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of Belcesiran; [8] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of August 2021

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

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

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis-PN*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Vutrisiran*	*hATTR Amyloidosis-PN*			●	Global
Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran*	*ATTR Amyloidosis*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Kidney Stones*	●	●		Global
Cemdisiran*	*Complement-Mediated Diseases*	●			50-50
Cemdisiran/Pozelimab Combo[6]*	*Complement-Mediated Diseases*	●			Milestone/Royalty
Belcesiran[7]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[8]*	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT)*	*Hypertension*	●			Global
ALN-HSD*	*NASH*	●			50-50

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of Belcesiran; [8] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of August 2021

Agenda

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

Introduction
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Primary Hyperoxaluria Type 1 Burden of Disease and Diagnosis
- Jeffrey M. Saland, MD, MSCR – Professor, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Recent Highlights, Lumasiran Program: Primary Hyperoxaluria Type 1 & Recurrent Stone Formers
- John Gansner, MD, PhD – Director, Clinical Research

Lumasiran Commercial Progress PH1
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Q&A Session

Primary Hyperoxaluria Type 1
Context and Overview

Jeffrey M. Saland, M.D.
Chief, Pediatric Nephrology & Hypertension
Mount Sinai Kravis Children's Hospital, NYC

Notes - Conflicts of Interest

This program is sponsored by Alnylam Pharmaceuticals

I am presenting on behalf of the company

I have received honoraria for my participation, and participated as an investigator in clinical trials studying lumasiran, and I have also received compensation for consulting services provided to Alnylam.

This is not a CME presentation

There will be a moderated Q&A at the end of this presentation. Questions will be reviewed by Alnylam

Goals: Context and Overview

Context:

- Introduction to kidney stone disease
- Discuss typical metabolic workup & hyperoxaluria

Overview:

- Discuss genetic testing
- Discuss Primary Hyperoxaluria Type 1

Kidney Stone Disease:

Lifetime Stone Prevalence (United States)

Characteristic	History of kidney stones, males	
	Unadjusted, % (95% CI)	Adjusted, % (95% CI)
All groups	10.6 (9.4–11.9)	10.3 (9.2–11.3)
Non-Hispanic, white	12.8 (11.3–14.3)	11.8 (10.4–13.2)
Hispanic	7.1 (5.7–8.4)	8.8 (7.4–10.2)
Non-Hispanic, black	4.5 (3.4–5.6)	4.8 (3.7–5.9)
Other race/multiracial	5.6 (2.5–8.8)	5.3 (2.2–8.5)

Characteristic	History of kidney stones, females	
	Unadjusted, % (95% CI)	Adjusted, % (95% CI)
All groups	7.1 (6.4–7.8)	6.7 (6.1–7.4)
Non-Hispanic, white	7.9 (7.0–8.8)	7.5 (6.7–8.4)
Hispanic	5.7 (4.6–6.9)	6.1 (4.9–7.3)
Non-Hispanic, black	4.2 (2.7–5.7)	4.2 (2.8–5.6)
Other race/multiracial	6.1 (2.7–9.6)	5.6 (2.4–8.8)

CI = confidence interval.

It's common:
~ 1 in 15 women &
~ 1 in 10 men
suffer a stone

Risk varies by

- **Sex**
- **Age (not shown)**
- **self-reported race (NHANES survey data)**

Scales CD Jr et al. Eur Urol. 2012 Jul;62(1):160-5

Kidney Stone Recurrence

Median ~15 per 100 person years (~ every 7 years)

But the rates are skewed:

- **After a first stone: 6 per 100 person-year (1 every 17 years)**
- **After > 1 stone: 16 per 100 person-year (1 every 6 years)**

Upshot:

- **one stone maybe bad luck**
- **2 stones or more, probably not bad luck**

Doesn't apply to kids, all should be considered abnormal

…. the stones also ;)

Ferraro PM et al. J Nephrol. 2017 Apr;30(2):227-233.

Kidney Stone Evaluation

Guidelines

- **First stone:**
  - review medical, dietary, & family history
  - Basic labs, analyze the stone (if caught)

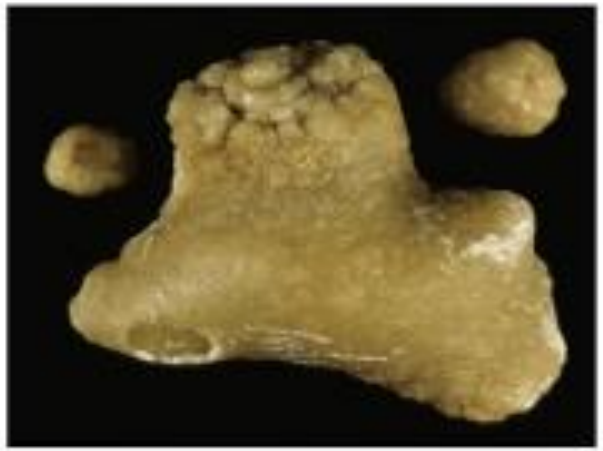
- **2 or more stones, risk factors*, children:**
  - full diagnostic evaluation

***Risk factors: family history, multiple stones at presentation, uncommon stone type, gastrointestinal disease, dietary risk, osteoporosis, nephrocalcinosis, reduced renal function**

Pearle MS et al. AUA guideline J Urol. 2014 Aug;192(2):316-24.
Williams JC Jr et al. “Urine and stone analysis…consensus..” Urolithiasis. 2021 Feb;49(1):1-16

PH1: Stone Analysis

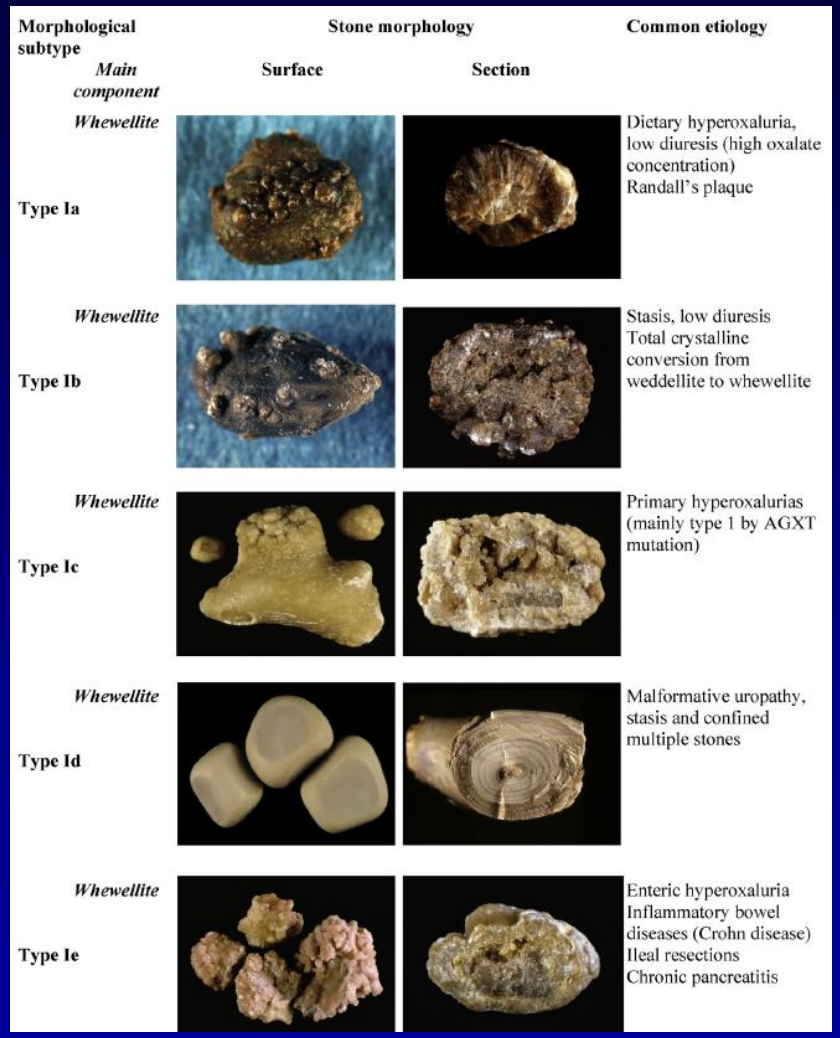
Nearly All Patients Have a Stone

Whewellite Type Ic			Primary hyperoxalurias (mainly type 1 by AGXT mutation)

Pure Calcium Oxalate (monohydrate) stones especially with a clear color instead of the usual dark color suggest primary Hyperoxaluria, and should prompt definitive diagnostic testing.

M. Daudon, et al. Comptes Rendus Chim, 19 (11–12) (2016), pp. 1470-1491

But… Ca-Oxalate Stones are Common



Stone composition and morphology is complex and occurs on a spectrum.

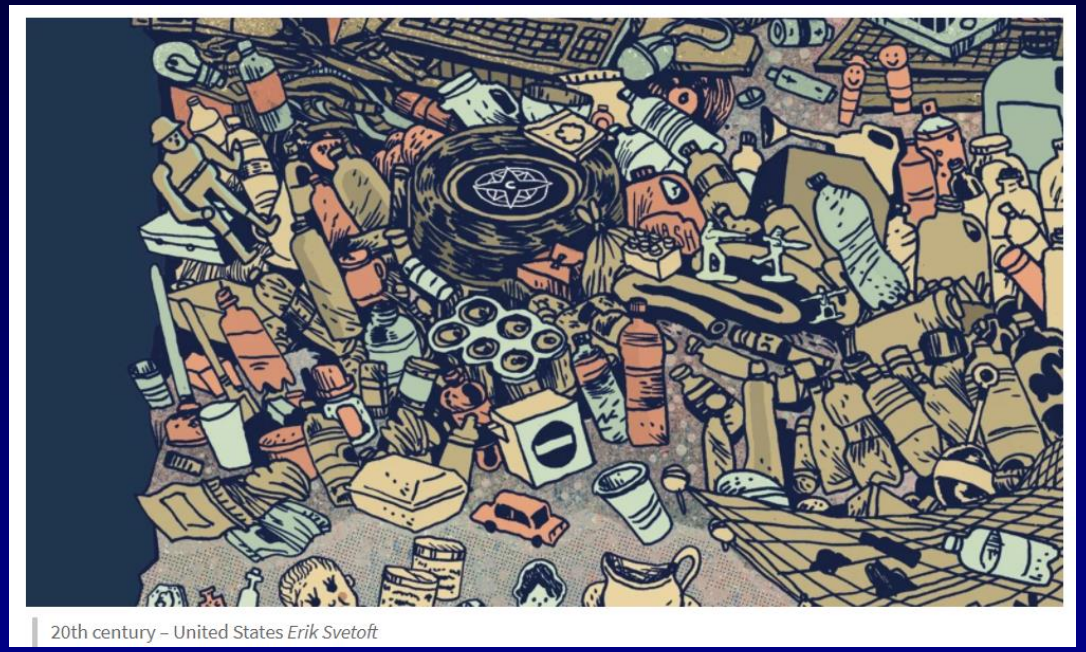
Such analysis alone is not reliable enough to rule-out a diagnosis and there are many clinical scenarios that can cause frequent Ca-oxalate stones.

M. Daudon, et al. Comptes Rendus Chim, 19 (11–12) (2016), pp. 1470-1491

Timed Urine Collection

AKA your waste tells a story!

18th century – New England *Erik Svetoft*



20th century – United States *Erik Svetoft*

Robert Short/CBC

J ROMEO Pop Science PUBLISHED APR 03, 2020 (drawings)

Timed Urine Collection

(Not A Popular Activity)
(And Needs Good Instruction)
(Usually 24 hours)

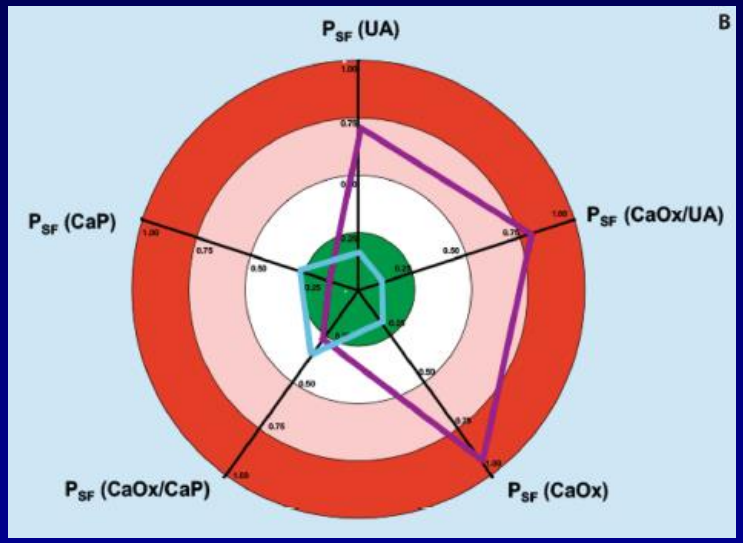
Timed Urine Collection (Metabolic Evaluation)

Stone Risk Factors / Cystine Screening: Not Performed **A**

DATE	SAMPLE ID	Vol 24	SS CaOx	Ca 24	Ox 24	Cit 24	SS CaP	pH	SS UA	UA 24
11/07/15	S16894029	2.61	5.48	305	37	600	1.41	6.322	0.36	0.903
08/15/15	S14276676	1.45	8.08	190	32	277	0.83	5.729	1.75	0.784
08/14/15	S16894027	1.32	11.90	205	41	308	1.24	5.874	1.57	0.828
REFERENCE RANGE		0.5 - 4L	6 - 10	male <250 female <200	20 - 40	male >450 female >550	0.5 - 2	5.8 - 6.2	0 - 1	male <0.800 female <0.750

Dietary Factors

DATE	SAMPLE ID	Na 24	K 24	Mg 24	P 24	Nh4 24	Cl 24	Sul 24	UUN 24	PCR
11/07/15	S16894029	299	73	70	1.109	29	287	40	13.08	1.3
08/15/15	S14276676	128	58	60	1.021	44	122	45	11.51	1.1
08/14/15	S16894027	138	52	69	0.923	36	133	40	10.59	1.1
REFERENCE RANGE		50 - 150	20 - 100	30 - 120	0.6 - 1.2	15 - 60	70 - 250	20 - 80	6 - 14	0.8 - 1.4



Williams JC Jr et al. “Urine and stone analysis…consensus..” Urolithiasis. 2021 Feb;49(1):1-16

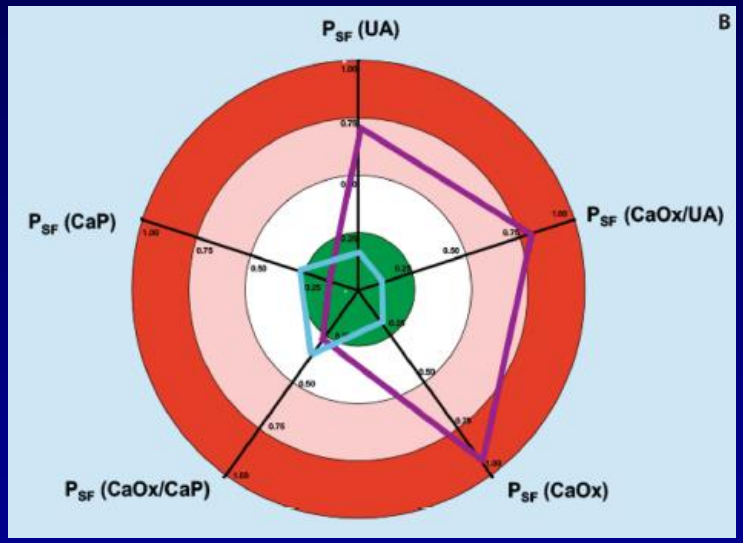
High Urine Oxalate = Hyperoxaluria :/

Stone Risk Factors / Cystine Screening: Not Performed — A

DATE	SAMPLE ID	Vol 24	SS CaOx	Ca 24	Ox 24	Cit 24	SS CaP	pH	S-S UA	UA 24
11/07/15	S16894029	2.61	5.48	305	37	600	1.41	6.322	0.36	0.903
08/15/15	S14276676	1.45	8.08	190	32	277	0.83	5.729	1.75	0.784
08/14/15	S16894027	1.32	11.90	205	41	308	1.24	5.874	1.57	0.828
REFERENCE RANGE		0.5 - 4L	6 - 10	male <250 female <200	20 - 40	male >450 female >550	0.5 - 2	5.8 - 6.2	0 - 1	male <0.800 female <0.750

Dietary Factors

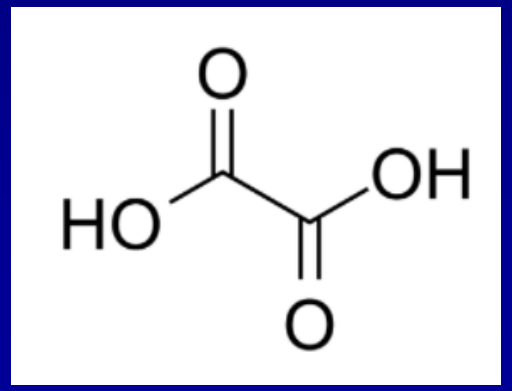
DATE	SAMPLE ID	Na 24	K 24	Mg 24	P 24	Nh4 24	Cl 24	Sul 24	UUN 24	PCR
11/07/15	S16894029	299	73	70	1.109	29	287	40	13.08	1.3
08/15/15	S14276676	128	58	60	1.021	44	122	45	11.51	1.1
08/14/15	S16894027	138	52	69	0.923	36	133	40	10.59	1.1
REFERENCE RANGE		50 - 150	20 - 100	30 - 120	0.6 - 1.2	15 - 60	70 - 250	20 - 80	6 - 14	0.8 - 1.4

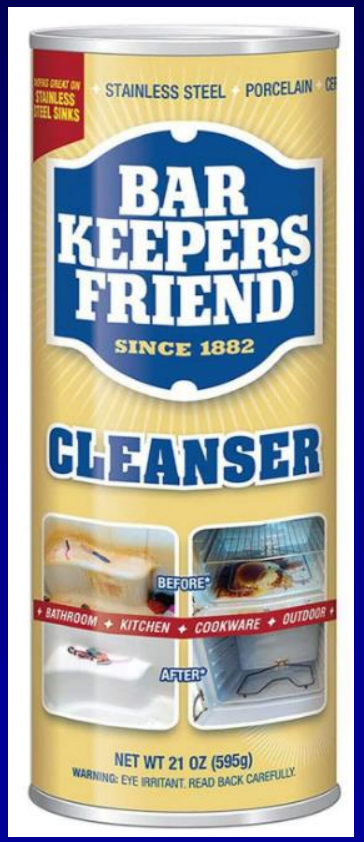


40 mg oxalate = 0.44 mMol
80 mg/day suggests PH

Williams JC Jr et al. “Urine and stone analysis…consensus..” Urolithiasis. 2021 Feb;49(1):1-16

Oxalate – Oxalic Acid





Combines well with Calcium and forms a highly insoluble molecule / crystal nidus (0.12 millimole/liter pure water at 37ºC)*

Temperature (°C)	Titration [10^{-4} M]	
	$[C_2O_4^{2-}]_{tot}$	σ
25	1.198	0.521
37	1.244	0.307
60	1.258	0.378
90	1.279	0.290

0.44 mmol needs 3.7L of water to dissolve

(urine has better solubility with stone inhibitors like citrate and Na, K, Mg, acids also– thank goodness for urine!)

* Ibas, F Et al. Crystals 2020, 10

Goals: Context and Overview

Context:

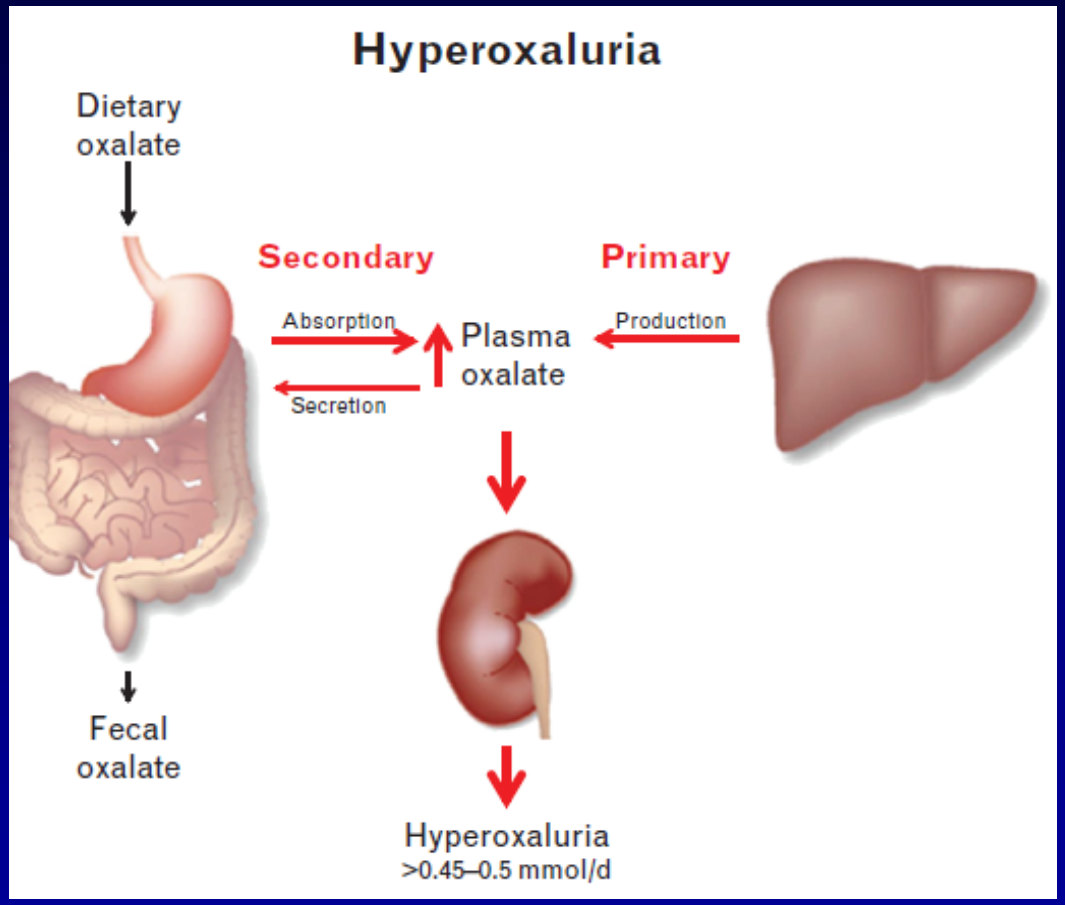
- Introduction to kidney stone disease
- Discuss typical metabolic workup & hyperoxaluria

Overview:

- Discuss genetic testing
- Discuss Primary Hyperoxaluria Type 1

Hyperoxaluria

Primary or Secondary (Enteric)



- History and physical
- Family history
- Dietary history
- Low Ca intake
- Intestinal diseases
- Fat malabsorption

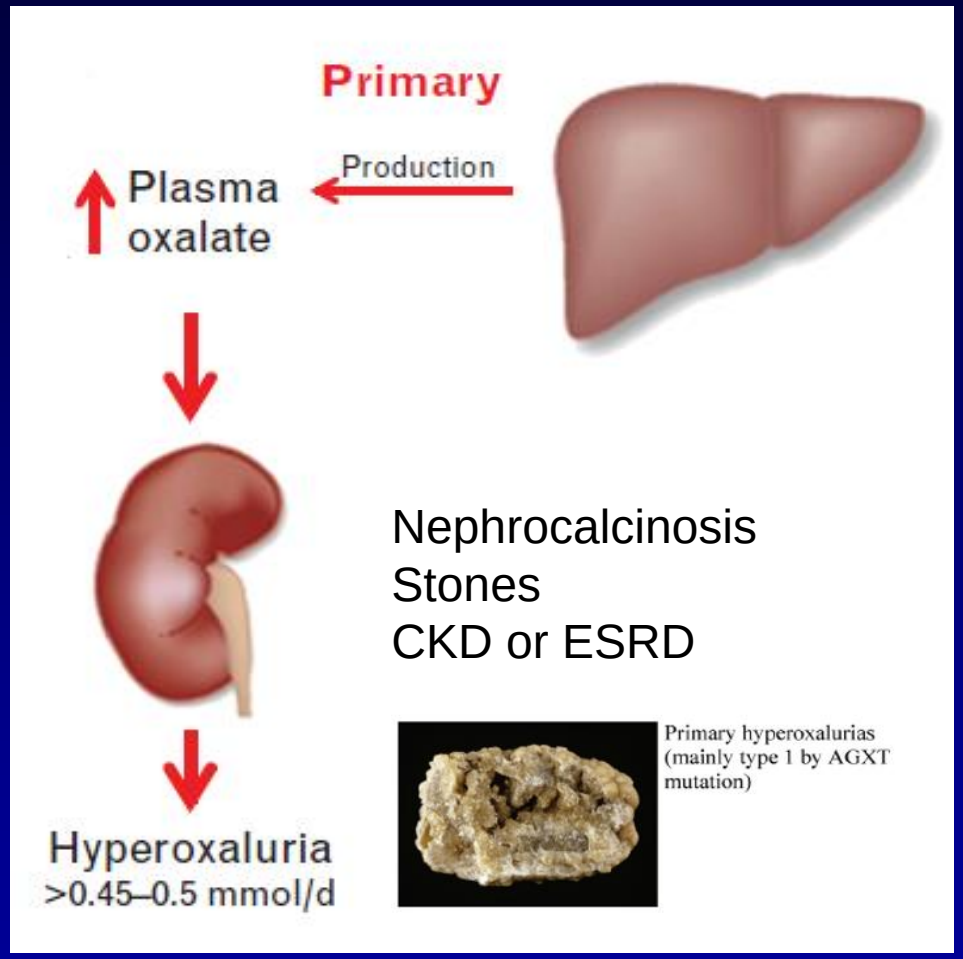
Genetic testing for PH

Per Rare Kidney Stone Consortium (RKSC) data:

- Identifies about 90% of cases

Ermer T. et al. Current opinion in nephrology and hypertension. 2016;25(4):363-371
Milliner DS et al updated 2017. GeneReviews® https://www.ncbi.nlm.nih.gov/books/
http://www.rarekidneystones.org/hyperoxaluria/physicians.html#registryhp (accessed Aug 2021)

Primary Hyperoxaluria Type 1 (PH1)



Genetic testing for PH

RKSC data:

- Identifies about 90%
- About 70% are PH1

Prevalence

- Historical 1-10 per million, higher regionally
- Likely underdiagnosed (clinical variability)
- Median diagnosis age in childhood
- Diagnosis possible at any age

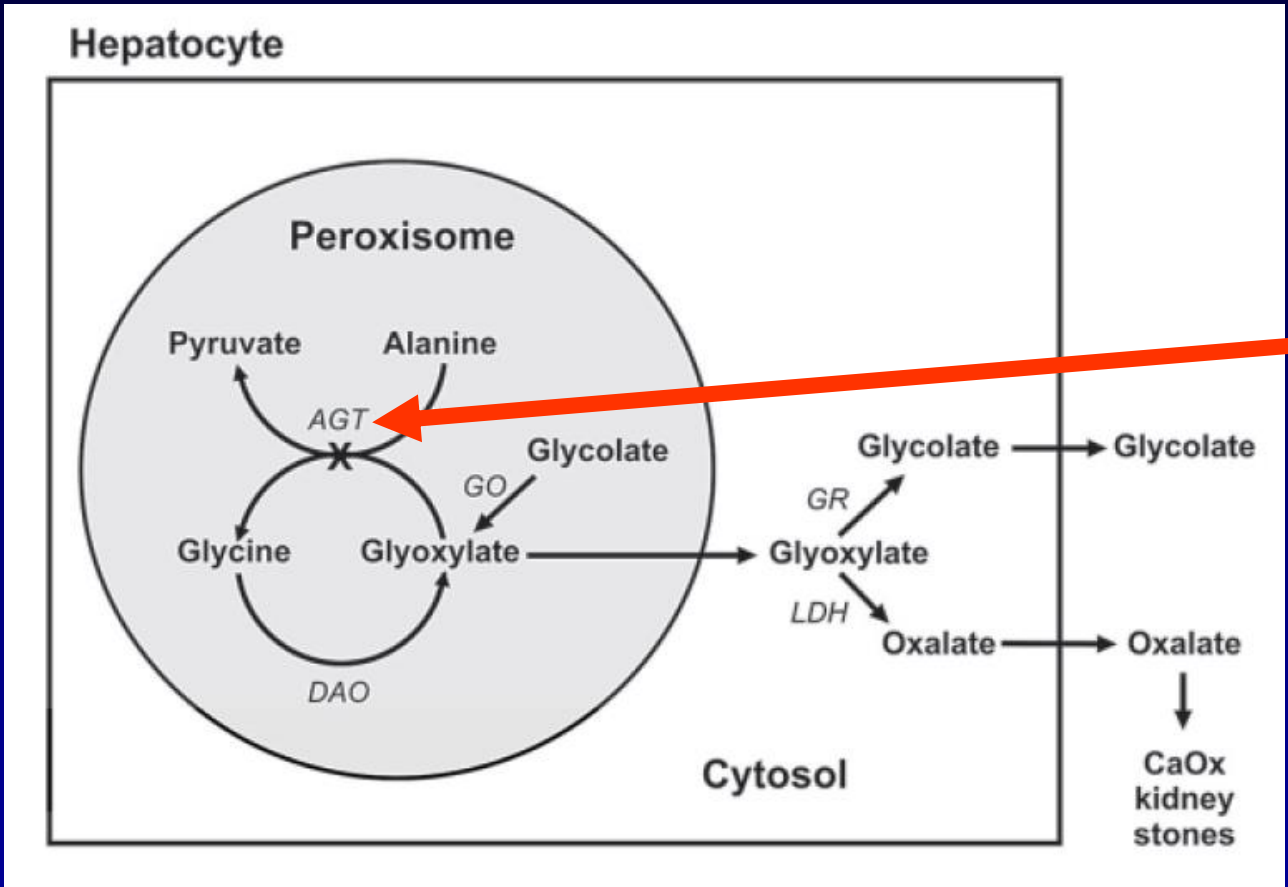
Genetic prevalence estimates:

- 1 in 150,000

Ermer T. et al. Current opinion in nephrology and hypertension. 2016;25(4):363-371
http://www.rarekidneystones.org/hyperoxaluria/physicians.html#registryhp (accessed Aug 2021)

Primary Hyperoxaluria Type 1

An Autosomal Recessive Disease



Glycolate is a normal product of metabolism.

Normally it's metabolized to glyoxylate then reacts with alanine to form pyruvate and glycine

In PH1, glyoxylate builds up and some gets metabolized to oxalate and some back to glycolate

Alanine:glyoxylate aminotransferase (product of *AGXT* gene); GR = glyoxylate reductase; GO = glycolate oxidase; LDH = lactate dehydrogenase; DAO = D-amino acid oxidase.

Danpure C, J: Nephron Exp Nephrol 2004

Primary Hyperoxaluria Type 1
Signs, Symptoms, Manifestations

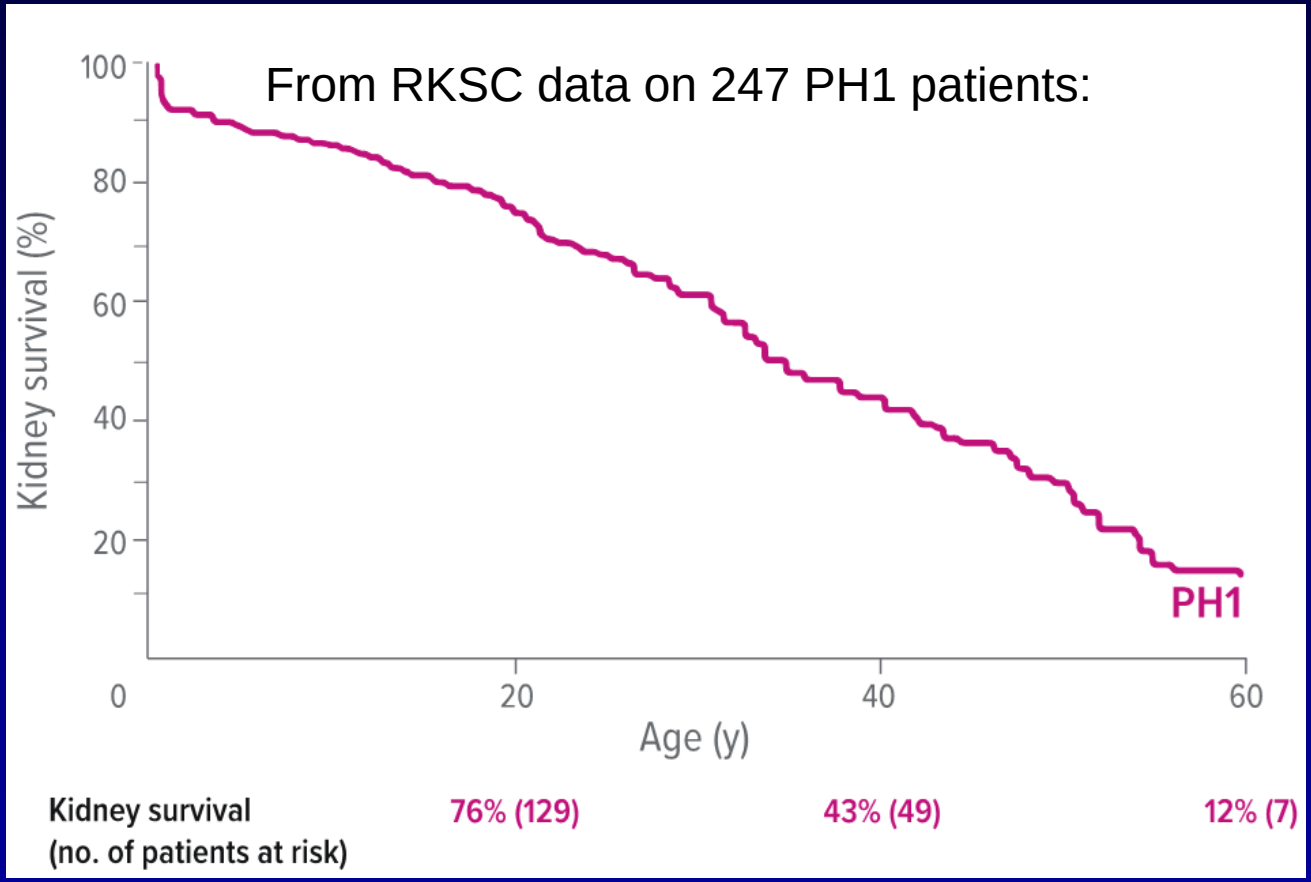
- Infantile: severe (poor growth, kidney failure)
- Nephrocalcinosis (widespread calcium oxalate deposition throughout the kidneys)
- Kidney stones
- Progressive CKD (chronic kidney disease) or failure

With lower (< about 30-45 ml/min/1.73m^2) kidney function, Systemic oxalosis occurs

- Bone / bone marrow
- Heart
- Skin
- Eye
- Thyroid, joints, muscle, others

Milliner DS et al updated 2017. GeneReviews® https://www.ncbi.nlm.nih.gov/books/

Primary Hyperoxaluria Type 1
Signs, Symptoms, Manifestations

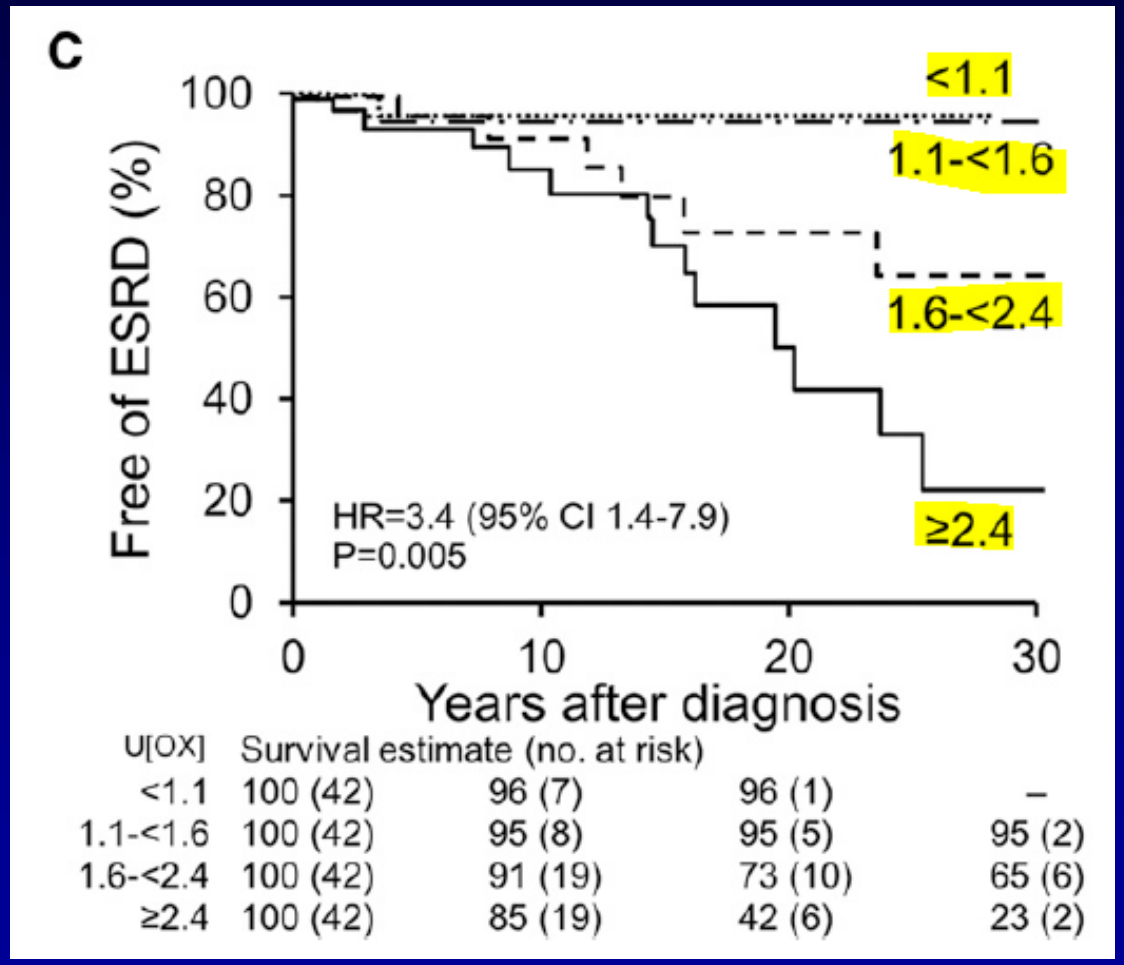


Progression to end-stage kidney disease (ESKD) can occur at different rates, but most patients eventually progress to kidney failure

- By age 35, about 50% of patients with PH1 have progressed to ESKD
- By age 60, about 90% of patients with PH1 will have progressed to ESKD
- Declines in kidney function can occur suddenly, even in patients with previously stable kidney function.

Hopp et al. JASN 2015;26:2559-2570
El-Reshaid K et al. Saudi J Kidney Dis Transpl. 2016;27(3):606-609

Primary Hyperoxaluria (all types)
Rate of Progression to Kidney Failure Depends on Uox



Renal survival was examined by quartile of urine oxalate excretion at diagnosis.

Among patients with PH who did not have ESRD at diagnosis, renal survival estimates at 10, 20, and 30 years were worst for those with Uox excretion ≥ 2.4 mmol/1.73m^2 per 24 hours

- (2.4 mmol = 211 mg)
- (1.6 mmol = 140 mg)
- PH1 patients' median ~ 2 mmol = 180 mg

HR, 3.4 for quartile Q4 vs quartiles Q1–Q3; 95% CI, 1.4 to 7.9

Zhao F, et al. Clin J Am Nephrol. 2016;11:119-126.

Primary Hyperoxaluria Type 1
Signs, Symptoms, Manifestations

- Diagnosis delays of years after symptom onset is common
- Up to 50% of adults diagnosed already have significant kidney disease
- 10% diagnosed after kidney failure sometimes after recurrence in a transplant !

Milliner DS et al updated 2017. GeneReviews® https://www.ncbi.nlm.nih.gov/books/

Primary Hyperoxaluria Type 1
Therapeutic Approaches to Prevent Complications

Hydration (Hyperhydration)

- Drinking large volumes of fluid at regular intervals over the entire day and night
- Dissolves calcium oxalate (prevents supersaturation)
- Small children may require a gastronomy or nasogastric tube to enable this
- 2-3 L/m^2 per 24 hours

Alkali citrate or pyrophosphate-containing solutions

- Inhibit calcium oxalate crystallization

Pyridoxine (Vitamin B6)

- About 30-50% of PH1 patients have significant (up to 30% Uox reduction) benefit
- p.Gly170Arg is associated with best B6 response

Dietary changes: of limited benefit

Milliner DS et al updated 2017. GeneReviews® https://www.ncbi.nlm.nih.gov/books/

Primary Hyperoxaluria Type 1
Other Treatments

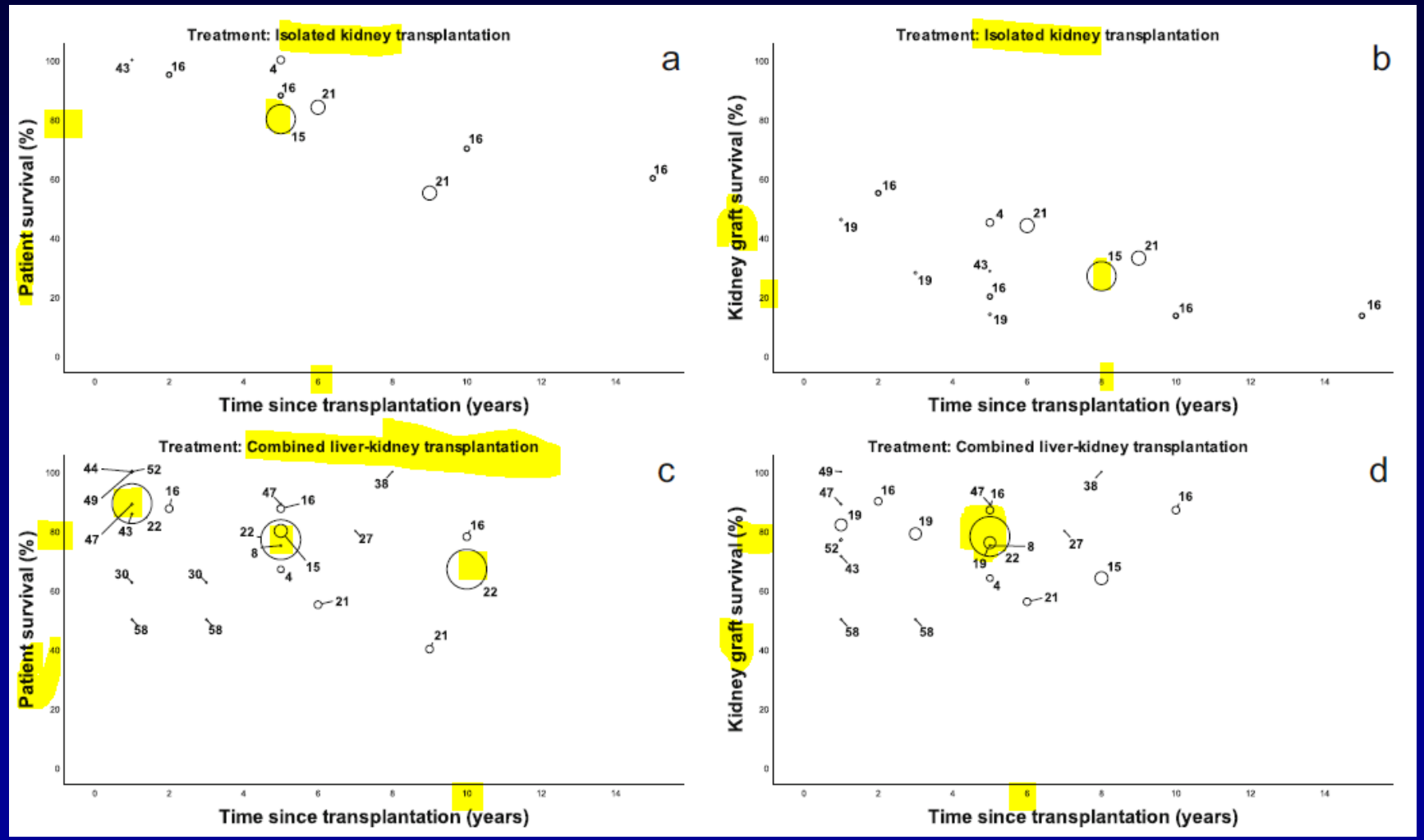
Stones
- Urological procedures
- Routine approaches to stone-related infections

Chronic kidney disease (CKD)
- Routine approaches to anemia, metabolic, cardiovascular complications

Kidney Failure
- Dialysis– not routine: need frequent, prolonged and still often inadequate
- Isolated kidney transplant (mobilization of oxalate and recurrence)
- Liver-kidney transplant (mobilization of oxalate, liver tx complications)

Milliner DS et al updated 2017. GeneReviews® https://www.ncbi.nlm.nih.gov/books/

Primary Hyperoxaluria Transplant Outcomes



Graft results very poor for kidney only, patient survival better for combined

Dialysis results would be worse

Metry EL et al. Pediatr Nephrol. 2021 Aug;36(8):2217-2226

Summary

- PH1 usually presents as a kidney stone disease
- Index of suspicion is needed, PH1 is rare, but also under-diagnosed
- Metabolic and genetic evaluation is readily available to diagnose PH1

- PH1 can result in significant morbidity from stones and their complications
- PH1 usually leads to kidney failure, especially when untreated
- Renal outcomes of PH are related to degree of urinary oxalate excretion
- Renal failure is a devastating outcome with systemic oxalosis risk

- Traditional treatments include “hyperhydration”, Vitamin B6, and crystal inhibitors
- Historical outcomes after kidney failure and transplant are challenging
- Historically observed outcomes highlight unmet needs for PH1 patients

Agenda

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

Introduction
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Primary Hyperoxaluria Type 1 Burden of Disease and Diagnosis
- Jeffrey M. Saland, MD, MSCR – Professor, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Recent Highlights, Lumasiran Program: Primary Hyperoxaluria Type 1 & Recurrent Stone Formers
- John Gansner, MD, PhD – Director, Clinical Research

Lumasiran Commercial Progress PH1
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Q&A Session

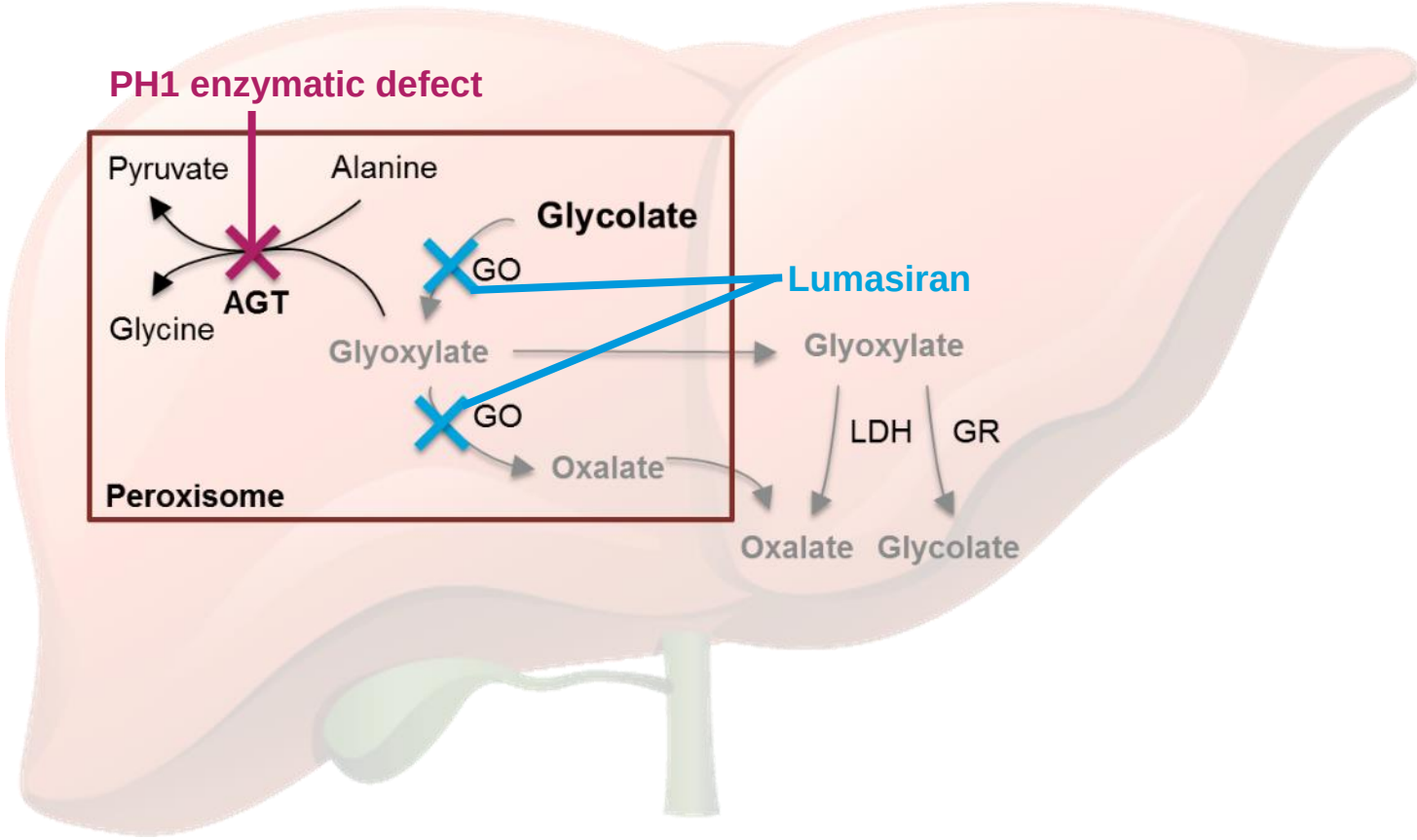
Lumasiran

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

Lumasiran:

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

Lumasiran Therapeutic Hypothesis:



HAO1, hydroxyacid oxidase 1

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

ILLUMINATE Phase 3 Program is Largest Clinical Development Program in PH1 to Evaluate Lumasiran Across all Ages and Full PH1 Disease Spectrum

ILLUMINATE•A

Double-blind, placebo-controlled *trial in PH1 patients* ***≥6 years old*** *with eGFR ≥30 mL/min/1.73m²*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1

ILLUMINATE•B

Single arm, open-label study in PH1 patients ***<6 years old*** *with eGFR >45 mL/min/1.73m²*

Primary endpoint results presented October 2020 ASN; Publication expected 2021

ILLUMINATE•C

Single arm, open-label study in PH1 patients with ***severe renal impairment*** *(eGFR<45)* ***including those on hemodialysis***

Topline results released July 2021; topline results for systemic oxalosis expected 2023

Phase 2 study in recurrent calcium oxalate kidney stone formers expected to initiate in 2021

ILLUMINATE•A Phase 3 Study Design

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

PATIENT POPULATION (N=39)

- Adults and children ≥6 years
- Urinary oxalate excretion ≥0.7 mmol/24hr/1.73m^2
- Confirmed *AGXT* mutations
- eGFR ≥30 mL/min/1.73m^2

2:1 RANDOMIZATION

6-MONTH DOUBLE-BLIND TREATMENT PERIOD

Lumasiran
qM × 3 loading dose, then q3M[a]
3.0 mg/kg subcutaneously

Placebo
qM × 3 loading dose, then q3M subcutaneously

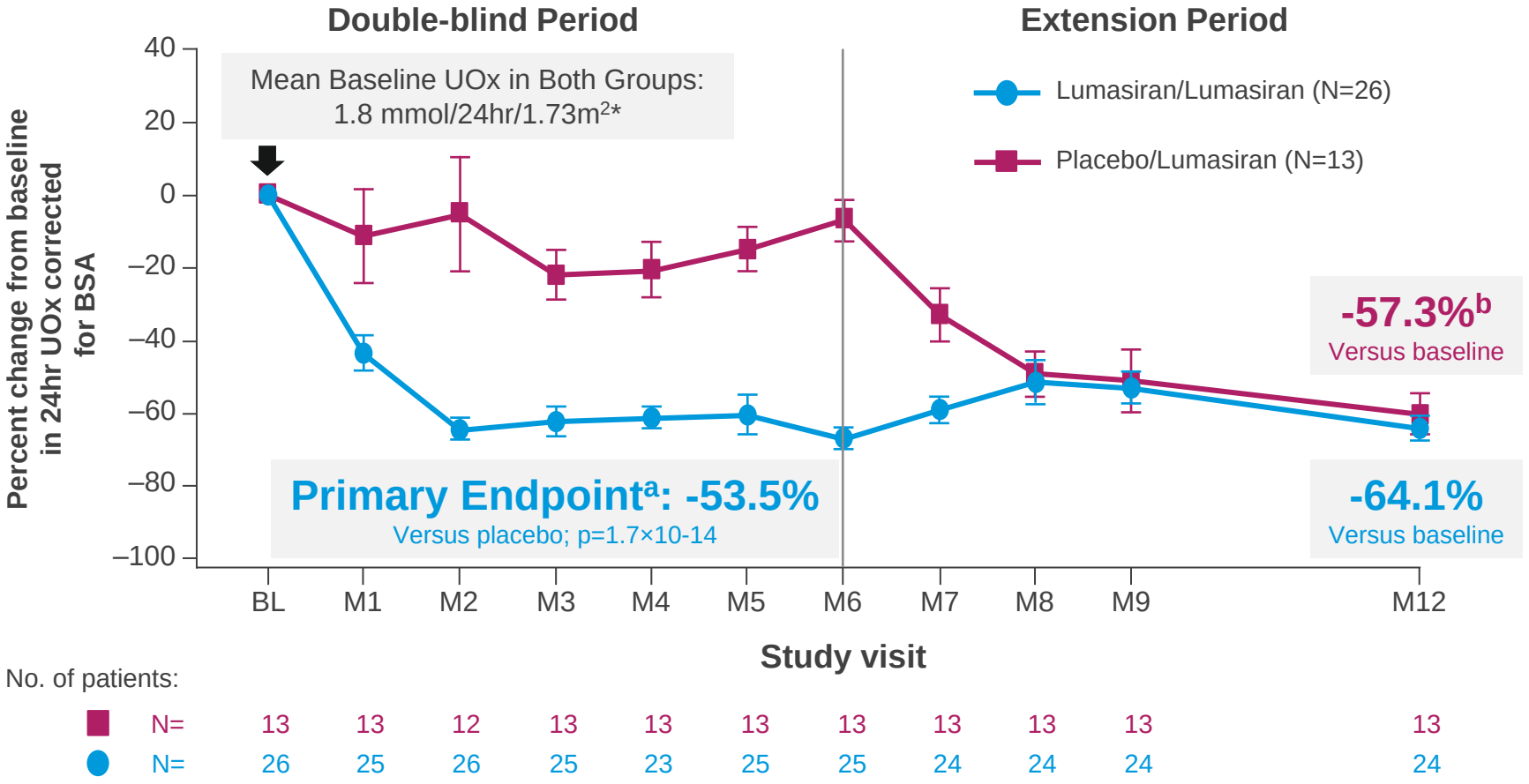
54-MONTH EXTENSION PERIOD

Lumasiran
q3M
3.0 mg/kg subcutaneously[b]

NCT03681184; EudraCT Number: 2018-001981-40

[a]Maintenance dose of 3.0 mg/kg (q3M) started 1 month after last loading dose. [b]Patients randomized to placebo received loading doses of 3.0 mg/kg lumasiran at Months 6, 7, and 8; patients randomized to lumasiran received a maintenance dose of 3.0 mg/kg lumasiran at Month 6, and placebo at Months 7 and 8. [c]1.70 mmol/24hr/1.73m^2= 153 mg/24hr/1.73m^2 (1 mmol/24hr/1.73m^2= 90 mg/24hr/1.73m^2)

ILLUMINATE•A Percent Change in 24hr Urinary Oxalate



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

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

Data in graph are mean ± SEM of observed values

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

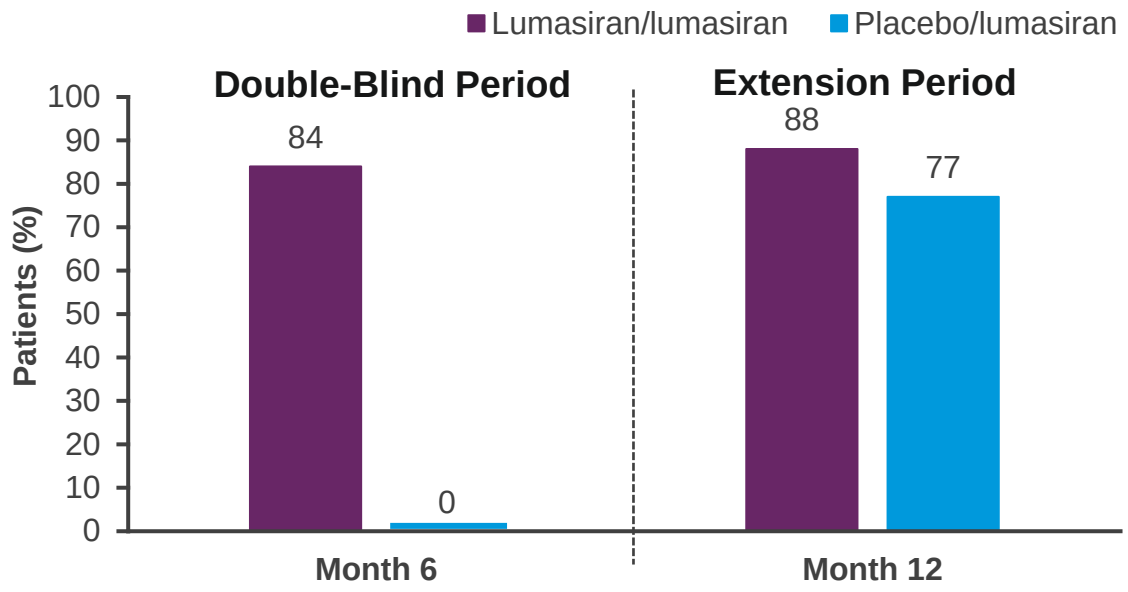
Adapted from Saland J et al. *American Society of Nephrology* 2020. Presentation PO2637.

ILLUMINATE•A Extension Period: Proportion of Patients with 24hr Urinary Oxalate Level ≤1.5×ULN

Comparable Proportion of Patients in the Placebo/Lumasiran Crossover Group Achieved Near Normalization or Normalization (≤1.5×ULN) of 24hr UOx After 6 Months of Treatment

84% of patients receiving lumasiran achieved near normalization or normalization (≤1.5×ULN) of 24hr UOx excretion at Month 6, compared with 0% of placebo-treated patients

77% of crossover patients achieved near normalization or normalization of 24hr UOx after 6 months of treatment*



Proportion of patients who achieved near normalization or normalization of 24-hour urinary oxalate was sustained through Month 12

*ULN=0.514 mmol/24hr/1.73m^2 for 24-hour UOx corrected for BSA

BSA, body surface area; ULN, upper limit of normal; UOx, urinary oxalate

Adapted from McGregor T et al. OxalEurope Meeting 2020. Presentation.

ILLUMINATE•A Safety Results with Ongoing Dosing

Safety Profile Remained Consistent at Month 12

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

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

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

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

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

Adapted from Saland J et al. *American Society of Nephrology* 2020. Presentation PO2637.

ILLUMINATE•B Phase 3 Study Design

Open-Label, Multicenter, Single-Arm Study in Young Patients with PH1

PATIENT POPULATION (N=18)

- Infants and children <6 years
- Elevated urinary oxalate:creatinine ratio
- Confirmed *AGXT* mutations
- eGFR >45 mL/min/1.73m^2 if ≥12 months old; normal serum creatinine if <12 months old

OPEN LABEL

6-MONTH PRIMARY ANALYSIS PERIOD

Lumasiran
qM × 3 loading dose, then qM or q3M maintenance dosing dependent on weight

54-MONTH EXTENSION PERIOD

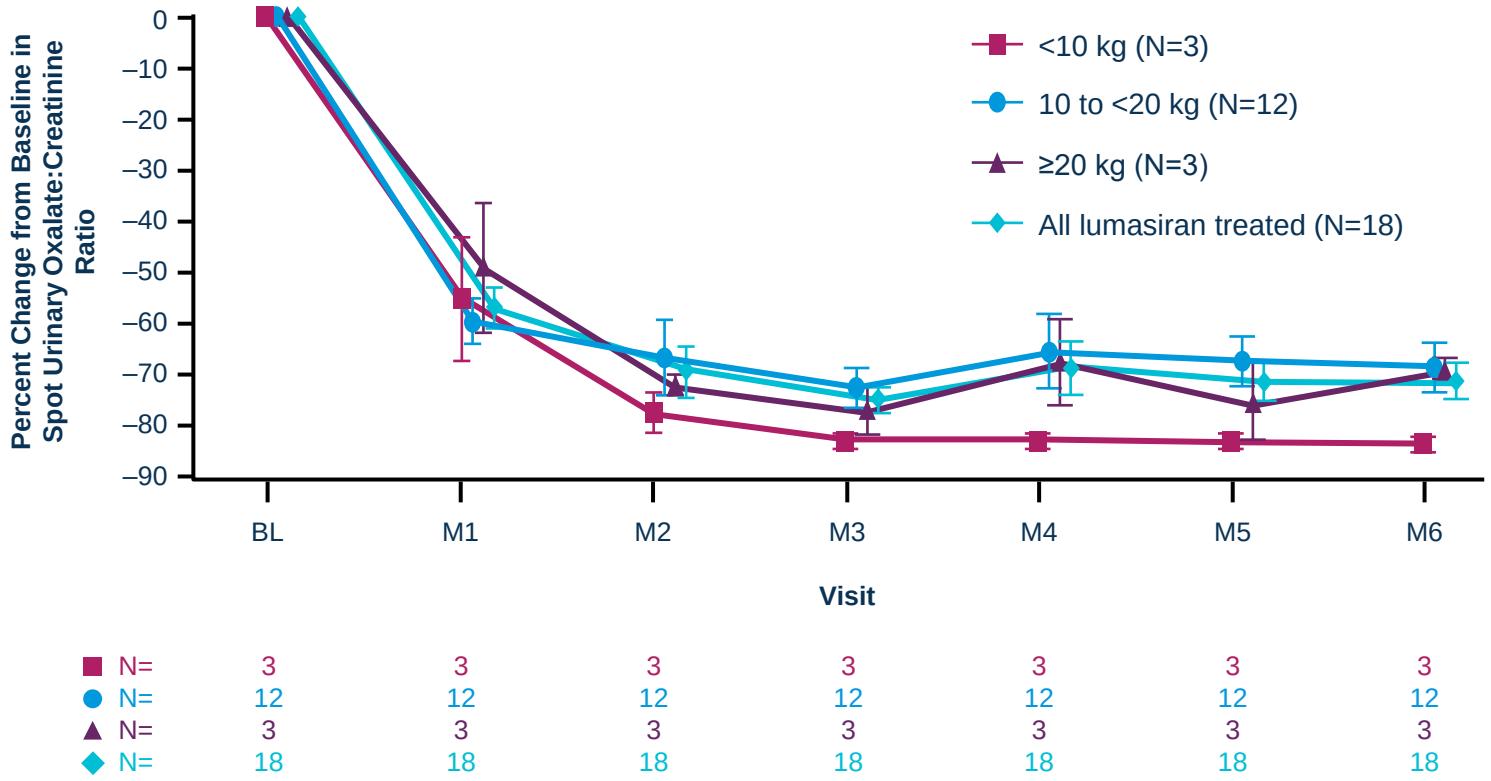
Lumasiran
qM or q3M maintenance dosing dependent on weight[a]

NCT03905694; EudraCT Number: 2018-004014-17

[a]Continued weight-based dosing using weight obtained 7 days prior to dosing

AGXT, alanine-glyoxylate aminotransferase gene; eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1; qM, monthly; qM × 3, once monthly for 3 consecutive months; qM, quarterly

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



-72.0%[a]
Versus baseline

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

[a]LS mean reduction from baseline to Month 6 (average of Month 3 through Month 6)
Data in graph are presented as mean ± SEM of observed values
BL, baseline; LS, least-squares; M, month; SEM, standard error of the mean; ULN, upper limit of normal
Adapted from Deschenes et al. *American Society of Nephrology* 2020. Presentation PO1624.

ILLUMINATE-B Safety Results

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

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

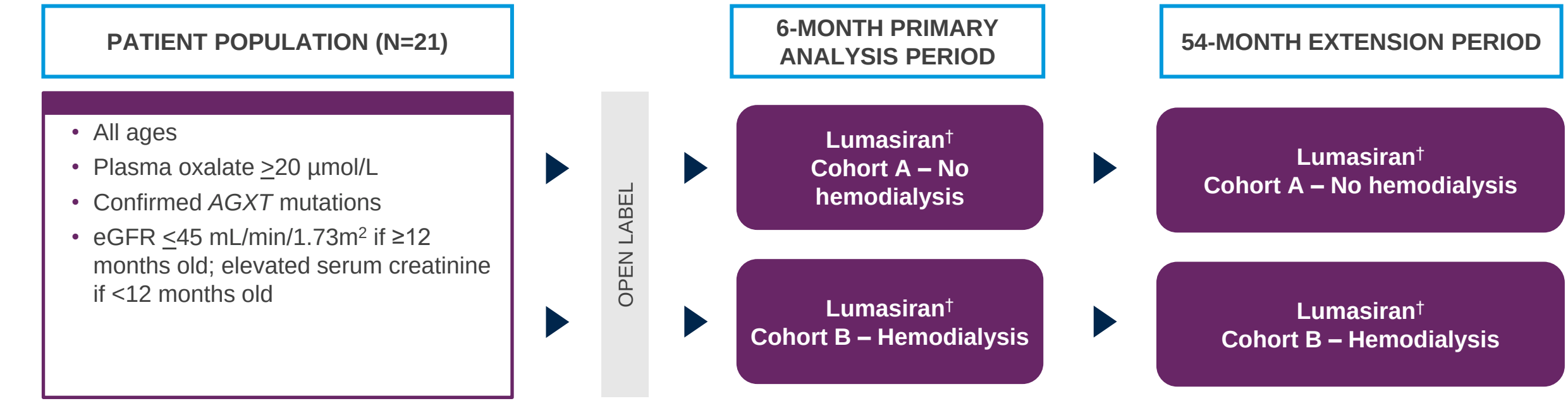
Safety data from first dose of lumasiran to data cut-off date: 30 June 2020.

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

Deschenes et al. *American Society of Nephrology* 2020. Presentation PO1624.

ILLUMINATE•C Lumasiran Phase 3 Study

Open-Label, Multicenter, Single-Arm Study in Patients with Advanced PH1



Topline results released July 2021; full results are expected to be presented at a medical meeting later this year

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

ILLUMINATE•C Topline Results

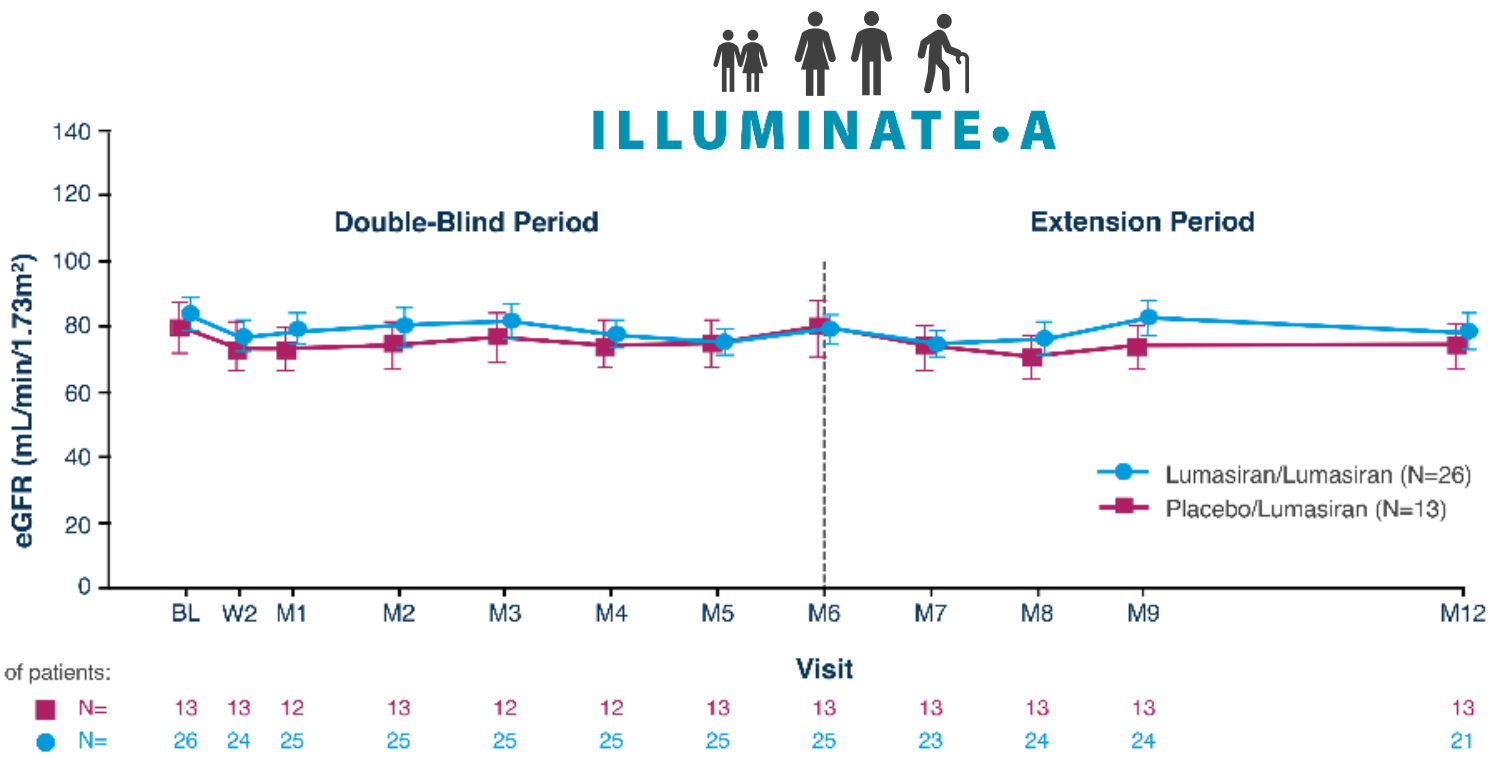
- **Lumasiran achieved substantial reductions in plasma oxalate relative to baseline**
  - In both dialysis-independent and -dependent patients

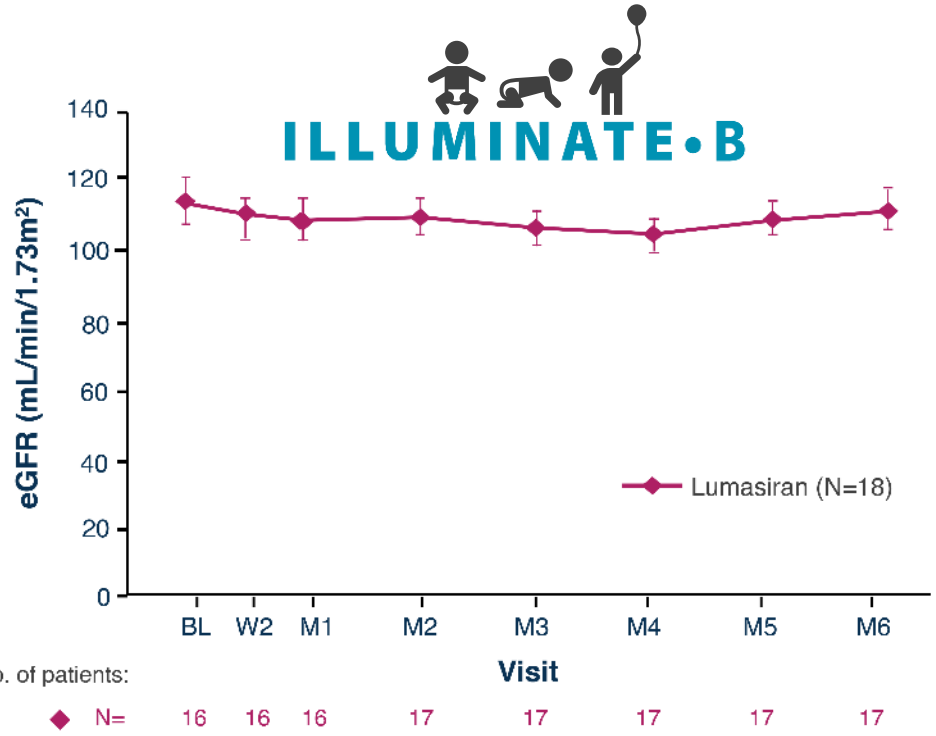
- **Lumasiran demonstrated an encouraging safety and tolerability profile**
  - No deaths or drug related SAEs
  - Most common AEs were ISRs in 5 patients (23.8%), all of which were mild
  - Two discontinuations due to AEs, both occurring during extension period and neither related to study drug

- **Supplemental regulatory filings expected to be submitted to FDA and EMA in late 2021**

eGFR from Baseline to Month 12 in ILLUMINATE-A and Baseline to Month 6 in ILLUMINATE-B

eGFR remained stable through the treatment period in both studies





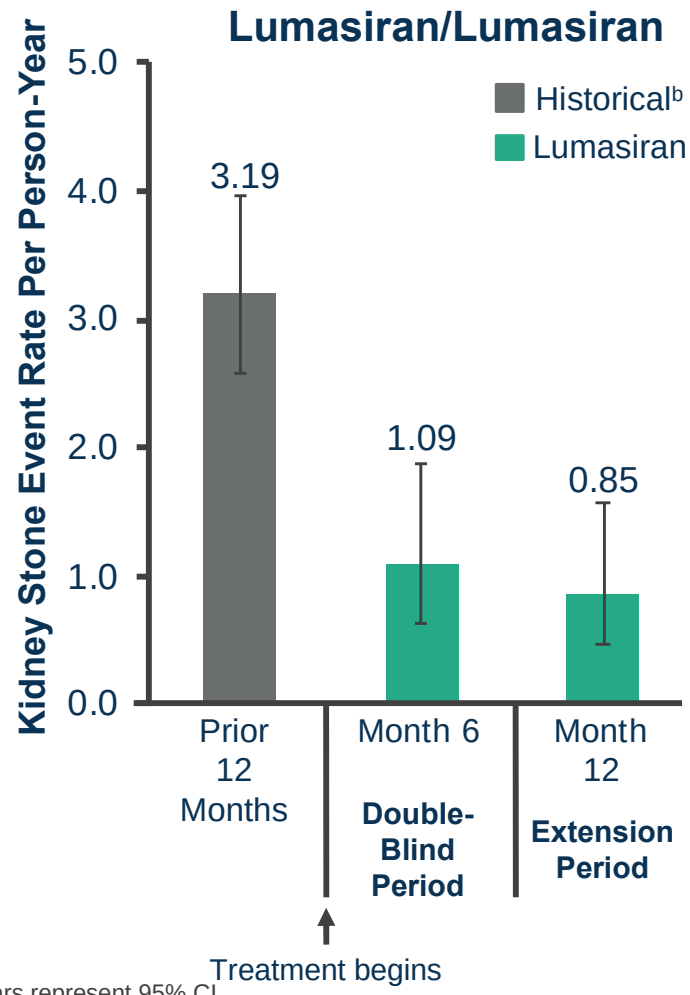
Change in eGFR from baseline was a secondary endpoint in both ILLUMINATE-A and ILLUMINATE-B

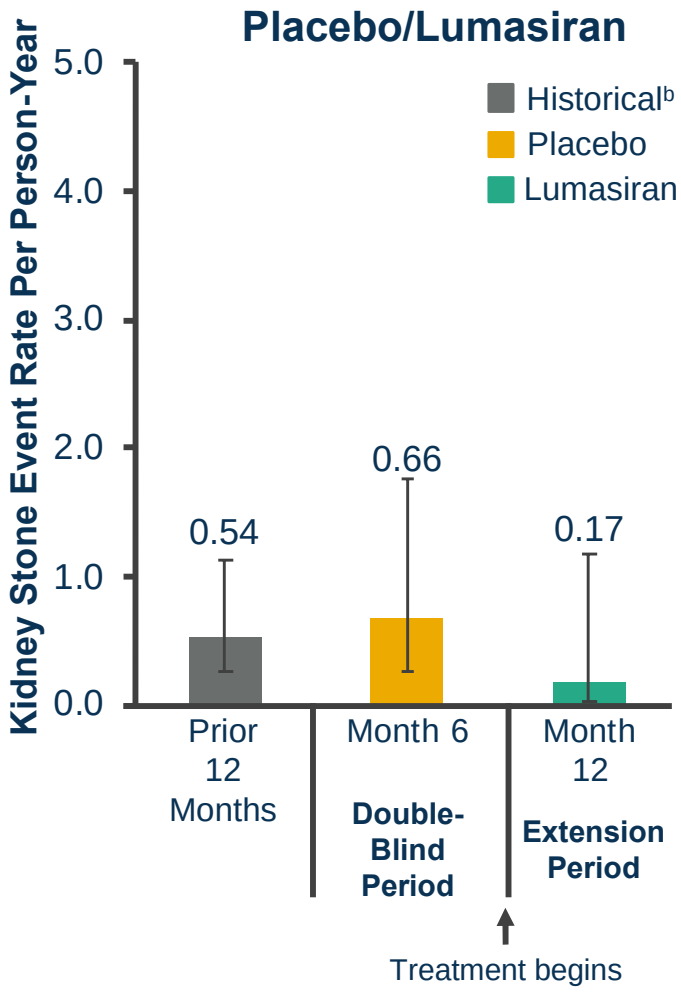
Data in graph are presented as mean ±SEM of observed values.

Sas et al. American Society of Pediatric Nephrology Annual Meeting 2021 E-PAS2021:EP-211.1940

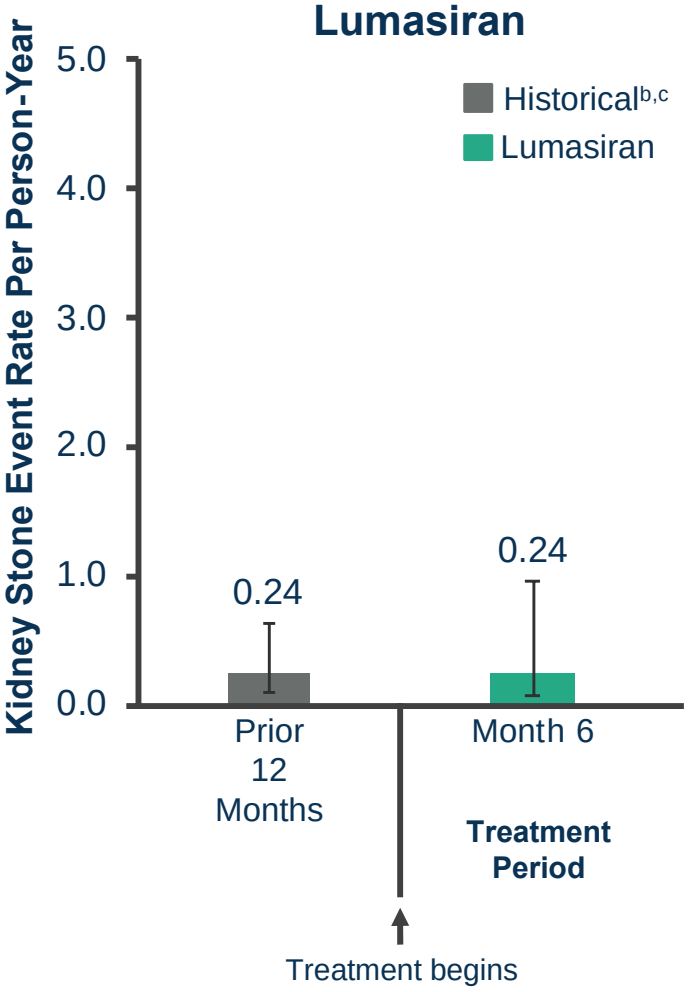
Exploratory Analysis of Kidney Stone Event Rates

ILLUMINATE-A[a]





ILLUMINATE-B



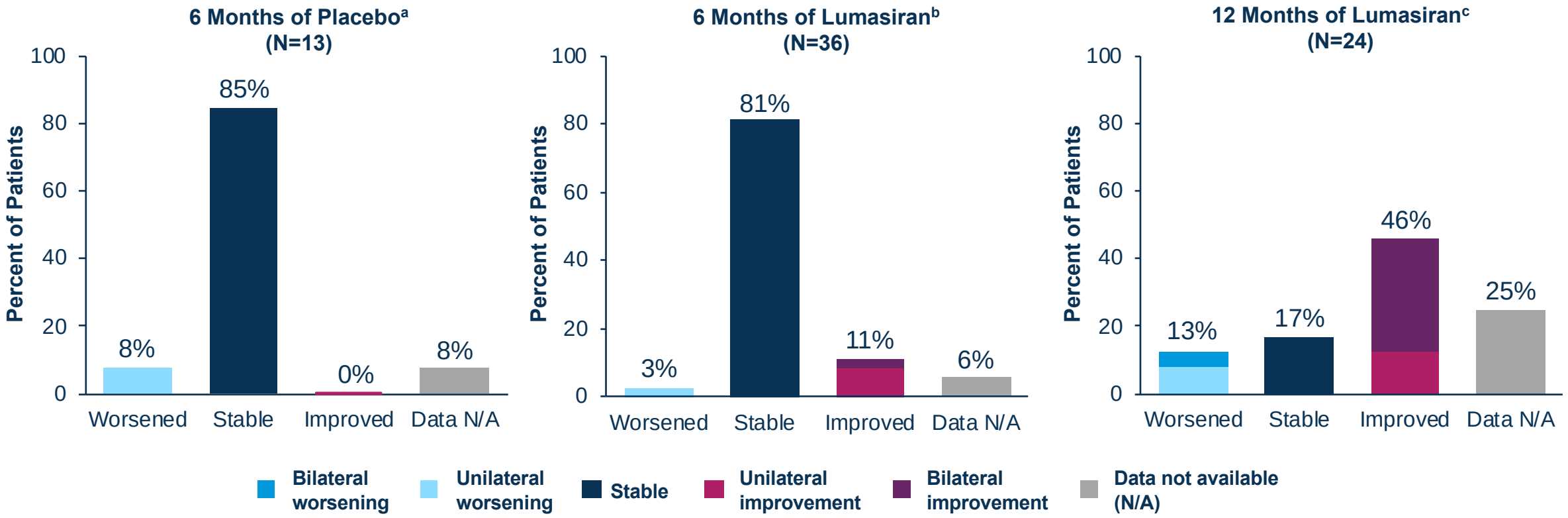
Error bars represent 95% CI.

[a]Randomization was not stratified by kidney stone events at baseline. [b]Patient reported history of kidney stone events. [c]Annualized rate was not calculated for patients <6 months old.

Sas et al. American Society of Pediatric Nephrology Annual Meeting 2021 E-PAS2021:EP-211.1940

ILLUMINATE-A Exploratory Analysis of Nephrocalcinosis

Nephrocalcinosis grade mostly stable or improved

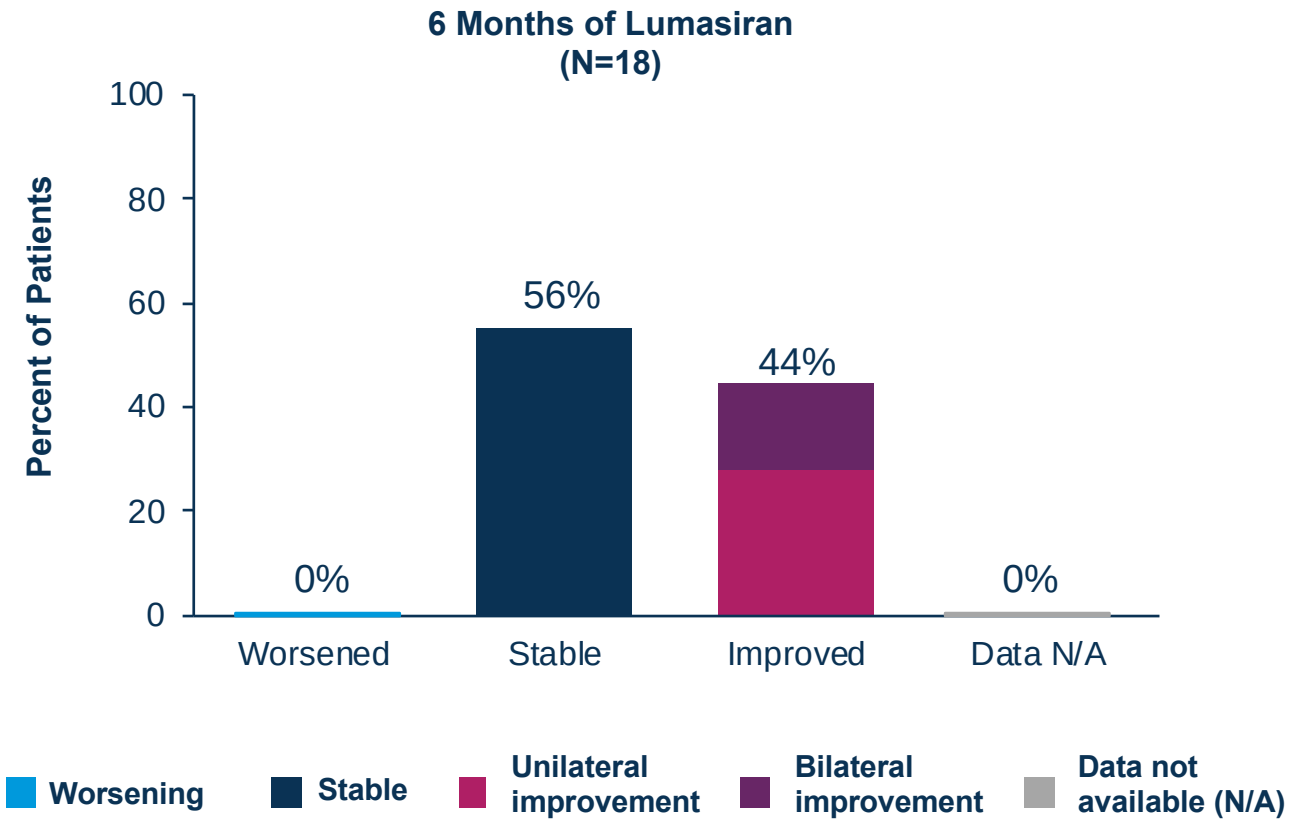


[a]Includes 6 months of placebo treatment for patients originally randomized to placebo. Data N/A for one patient who had kidney ultrasound at Month 6, but the images were not adequate for grading nephrocalcinosis. [b]Includes first 6 months of treatment for patients originally randomized to lumasiran and the first 6 months of lumasiran treatment for patients originally randomized to placebo. Data N/A for 2 patients who did not have kidney ultrasound after 6 months of lumasiran treatment. [c]Includes 12 months of treatment for patients originally randomized to lumasiran. Data N/A for 4 patients who did not have kidney ultrasound after 12 months of lumasiran treatment, for 1 patient who discontinued treatment, and for 1 patient who withdrew from the study. Two patients in the lumasiran group did not have valid kidney ultrasounds at baseline and were excluded from the current analysis. One placebo crossover patient did not have kidney ultrasound before the first dose of lumasiran and was also excluded from the current analysis.

Sas et al. American Society of Pediatric Nephrology Annual Meeting 2021 E-PAS2021:EP-211.1940

ILLUMINATE•B Exploratory Analysis of Nephrocalcinosis

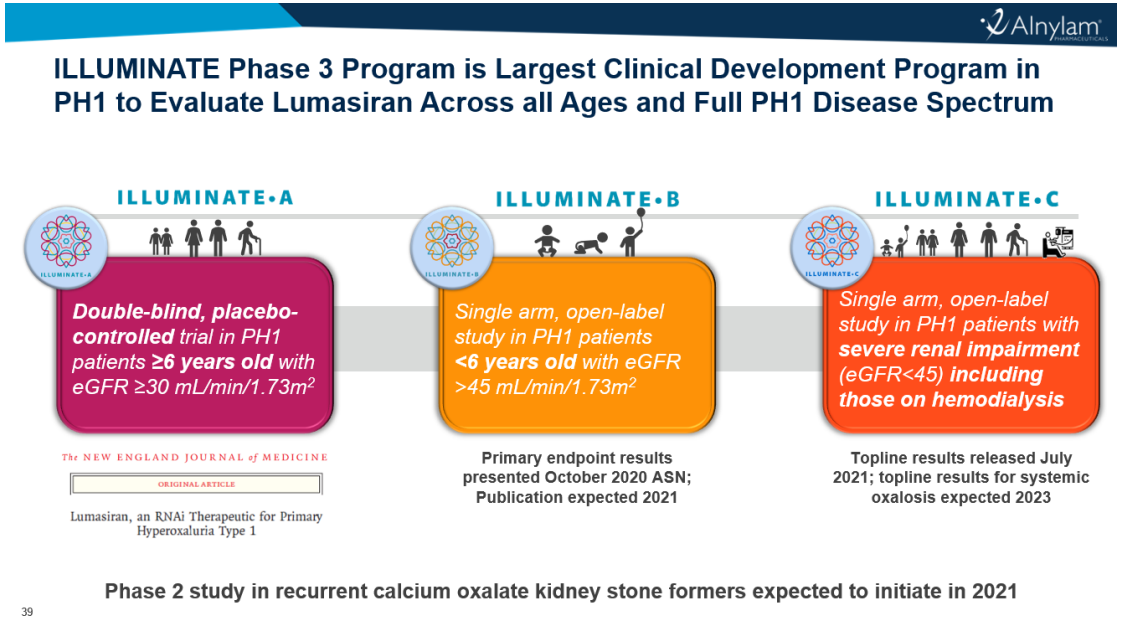
Nephrocalcinosis grade stable or improved



Sas et al. American Society of Pediatric Nephrology Annual Meeting 2021 E-PAS2021:EP-211.1940

Conclusions

- Largest clinical development program in PH1 across all patient types
- Significant and sustained lowering of UOx in infants, children and adults with preserved renal function in ILLUMINATE-A and B
- Substantial reduction of POx in patients with severe renal impairment including those on hemodialysis in ILLUMINATE-C
- Encouraging signs of improved clinical outcomes and measures in an otherwise progressive disease with stable eGFR, reduction in kidney stones and improvement in nephrocalcinosis grade
- Encouraging safety and tolerability profile
- ILLUMINATE-C topline results on systemic oxalosis endpoints expected 2023



Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

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

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis-PN*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Vutrisiran*	*hATTR Amyloidosis-PN*			●	Global
Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran*	*ATTR Amyloidosis*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* ***Recurrent Kidney Stones***	●	●		Global
Cemdisiran*	*Complement-Mediated Diseases*	●			50-50
Cemdisiran/Pozelimab Combo[6*]	*Complement-Mediated Diseases*	●			Milestone/Royalty
Belcesiran[7*]	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[8*]	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT)*	*Hypertension*	●			Global
ALN-HSD*	*NASH*	●			50-50

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of Belcesiran; [8] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of August 2021

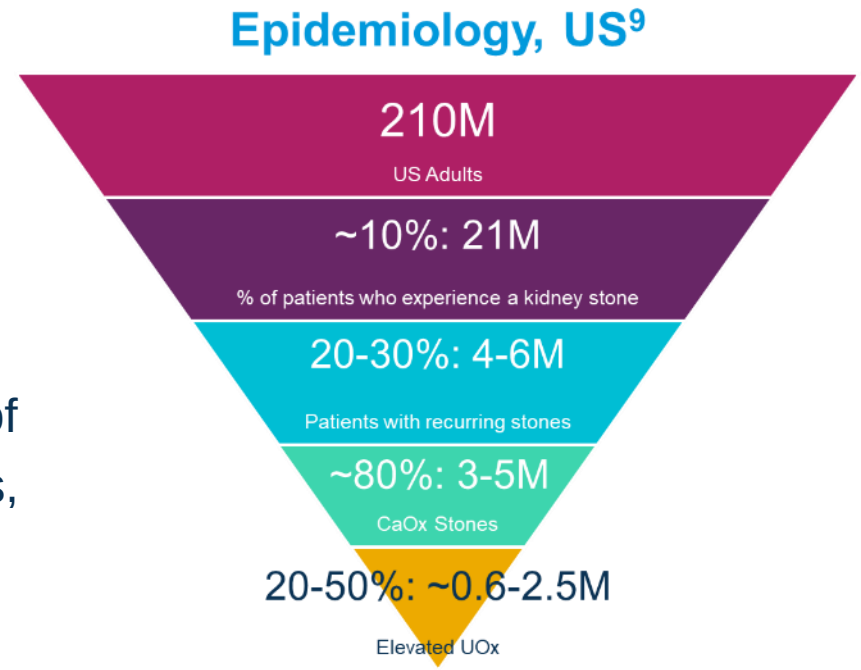
Recurrent Calcium Oxalate Kidney Stone Disease

Prevention of stone recurrence offers an opportunity to avoid painful stone episodes and invasive procedures[1]

- Recurrent kidney stone disease is associated with significant clinical burden including pain, infection/sepsis, hospitalizations, and a greater risk for developing chronic kidney disease (CKD) and end stage kidney disease[2-4]

- There are limited effective treatment options and despite best standard of care (dietary/lifestyle changes, citrate supplementation, thiazide diuretics, etc.) recurrent stones still occur[5,6]

- Approximately 80% of kidney stones in adults are formed from calcium oxalate crystals with up to 2.5 million Americans having recurrent calcium oxalate stone disease with elevated urinary oxalate[7-9]



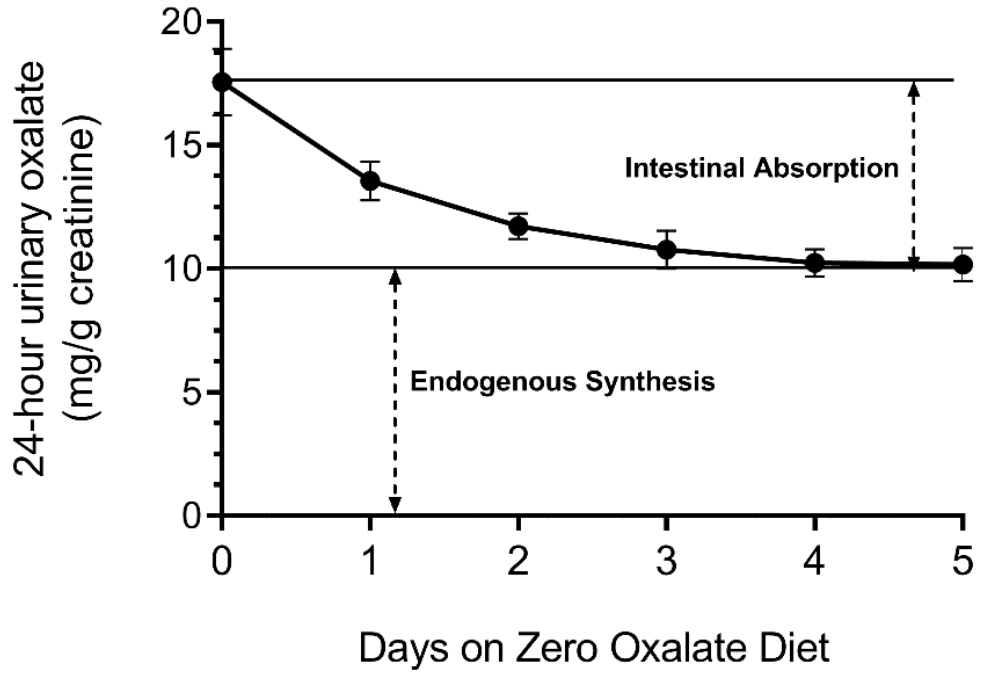
1. Beara-Lasic and Goldfarb, Clin J Am Soc Nephrol 2019. 2. Dhondup, Am J Kidney Dis, 2018. 3. Rule, Clin J Am Soc Nephrol, 2009. 4. Alexander et al., BMJ 2012. 5. Pearle et al., AUA Guideline 2014. 6. Türk et al., EAU Guidelines on Urolithiasis 2021. 6. Curhan, Urol Clin North Am, 2007. 7. Worcester and Coe, Prim Care 2008. 8. Worcester and Coe, NEJM 2010. 9. Internal estimates based on multiple data sources.

CKD, chronic kidney disease; M, million; UOx, urinary oxalate

Lumasiran Life-cycle Management: Proof-of-concept Phase 2 in Recurrent Stone Former Population

- **Rationale:**
  - Approximately 80% of kidney stones in adults are formed from calcium oxalate crystals[1-2]
  - Stone formation occurs when a supersaturating level of calcium oxalate is present in the urine[3-4]
  - Liver production of oxalate is expected to be a significant driver of high urinary oxalate based on a healthy volunteer study[4]
  - Lumasiran is designed to reduce hepatic production of oxalate through inhibition of GO[5]
- **Population:** Recurrent calcium oxalate kidney stone disease and elevated 24-hour urinary oxalate levels
  - Excludes patients with secondary causes of elevated urinary oxalate/recurrent kidney stones
- **Primary Endpoint:** Percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
- **Expected to initiate in 2021**

Endogenous oxalate is >50% based on healthy volunteer study[4]



1. Worcester and Coe, Prim Care 2008. 2. Worcester and Coe, NEJM 2010. 3. Coe et al., Nat Rev Nephrol 2016. 4. Mitchell et al., Am J Physiol Renal Physiol 2019. 5. Liebow et al., J Am Soc Nephrol 2017.

GO, glycolate oxidase

Agenda

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

Introduction
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Primary Hyperoxaluria Type 1 Burden of Disease and Diagnosis
- Jeffrey M. Saland, MD, MSCR – Professor, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Recent Highlights, Lumasiran Program: Primary Hyperoxaluria Type 1 & Recurrent Stone Formers
- John Gansner, MD, PhD – Director, Clinical Research

Lumasiran Commercial Progress PH1
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Q&A Session

OXLUMO® (lumasiran) Market Opportunity

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

PREVALENCE	DIAGNOSIS	DISEASE BURDEN	COST BURDEN
~3,000	**~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[2]	average cost (transplant & lifelong immunosuppression)

OXLUMO | PRIMARY HYPEROXALURIA TYPE 1

>$500M potential market opportunity

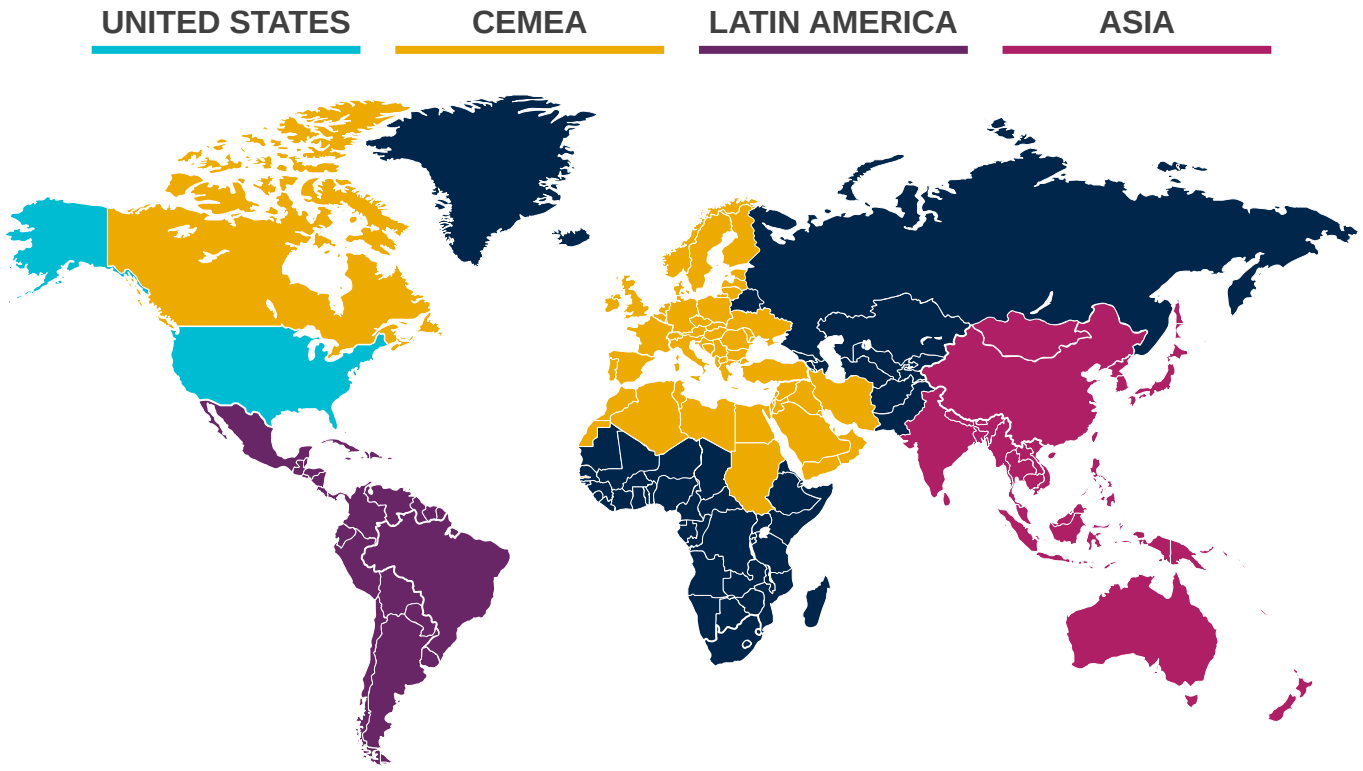
[1] Hopp R, et al. J Am Soc Nephrol. 2015;26:2559-2570

[2] Harambat J, et al. Kidney Int. 2010;77(5):443-449

OXLUMO Global Commercialization

Ensuring Availability Around the World

- Now approved in US, EU and Brazil
- Launched in USA and Germany
- Named patient sales in France and other markets
- Additional EU launches underway in Netherlands and Luxembourg in 2021 and Italy, Spain and Belgium expected in 2022.
- Partnerships in Israel and Turkey to provide access to OXLUMO in 2021 and 2022
- Continued global regulatory filings and launches planned across regions



OXLUMO™ (lumasiran) for injection 94.5 mg/0.5 mL

CEMEA: Canada, Europe, Middle East, North Africa

OXLUMO® Launch Update: Q2 2021

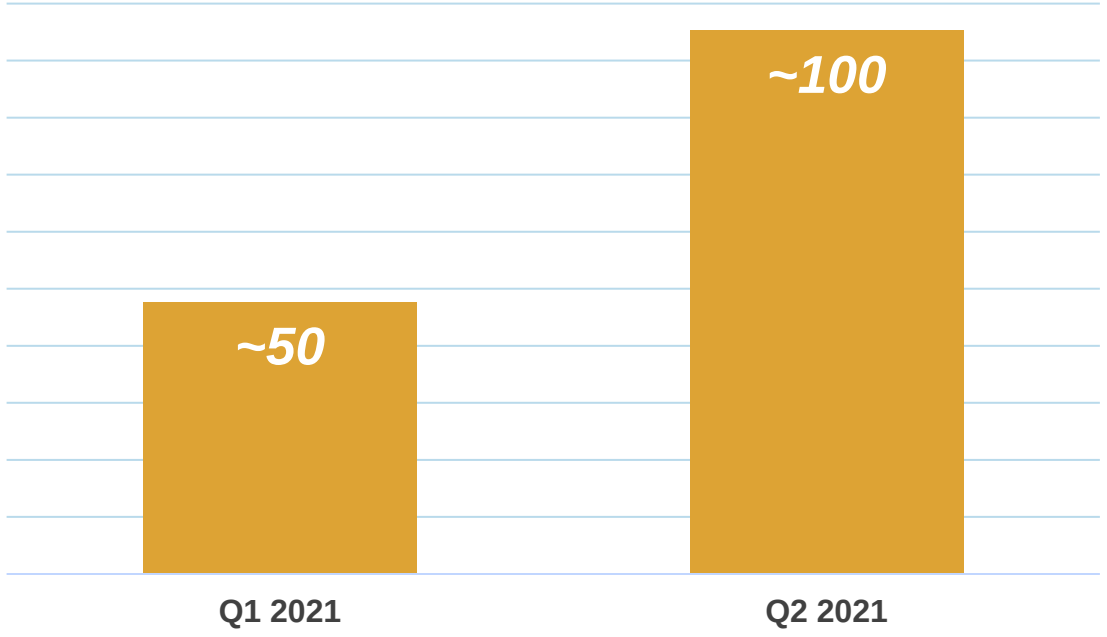
Strong Second Quarter Performance with Broad Utilization across Age Groups and eGFR Categories

$16M

OXLUMO Global Q2 2021 Net Product Revenues

~100

Patients Worldwide on Commercial OXLUMO at end of Q2 2021



Q2 U.S. Highlights

7 Value-Based Agreements (VBAs) finalized

>80% covered U.S. lives with confirmed access to OXLUMO, if prescribed

Start Forms are an incomplete picture of U.S. demand. 2021 Managed Healthcare Executive® Pharmacy Survey: Drugs New to the Market Most Likely to Reduce Morbidity, Mortality. **MHE Publication**, MHE June 2021, Volume 31, Issue 6

Bringing RNAi Therapeutics to Patients Worldwide

Robust Medical Affairs and Commercial Platform Leverageable for Continued Success

Strong Product Profile & First to market

The NEW ENGLAND JOURNAL of MEDICINE

Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1

takeonph1.com

era edta

Oxalosis & Hyperoxaluria Foundation

STEPPING STONES TO A CURE

Engagement and Advocacy

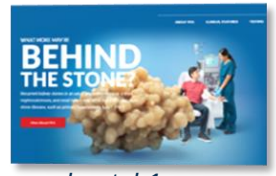
ASN American Society of Nephrology

RARE KIDNEY STONE CONSORTIUM

OXALEUROPE

American Urological Association

Education



aboutph1.com

Medscape

PeerVoice

medthority

Business Excellence

AlnylamAct®

GeneAct™

Diagnosis

Access

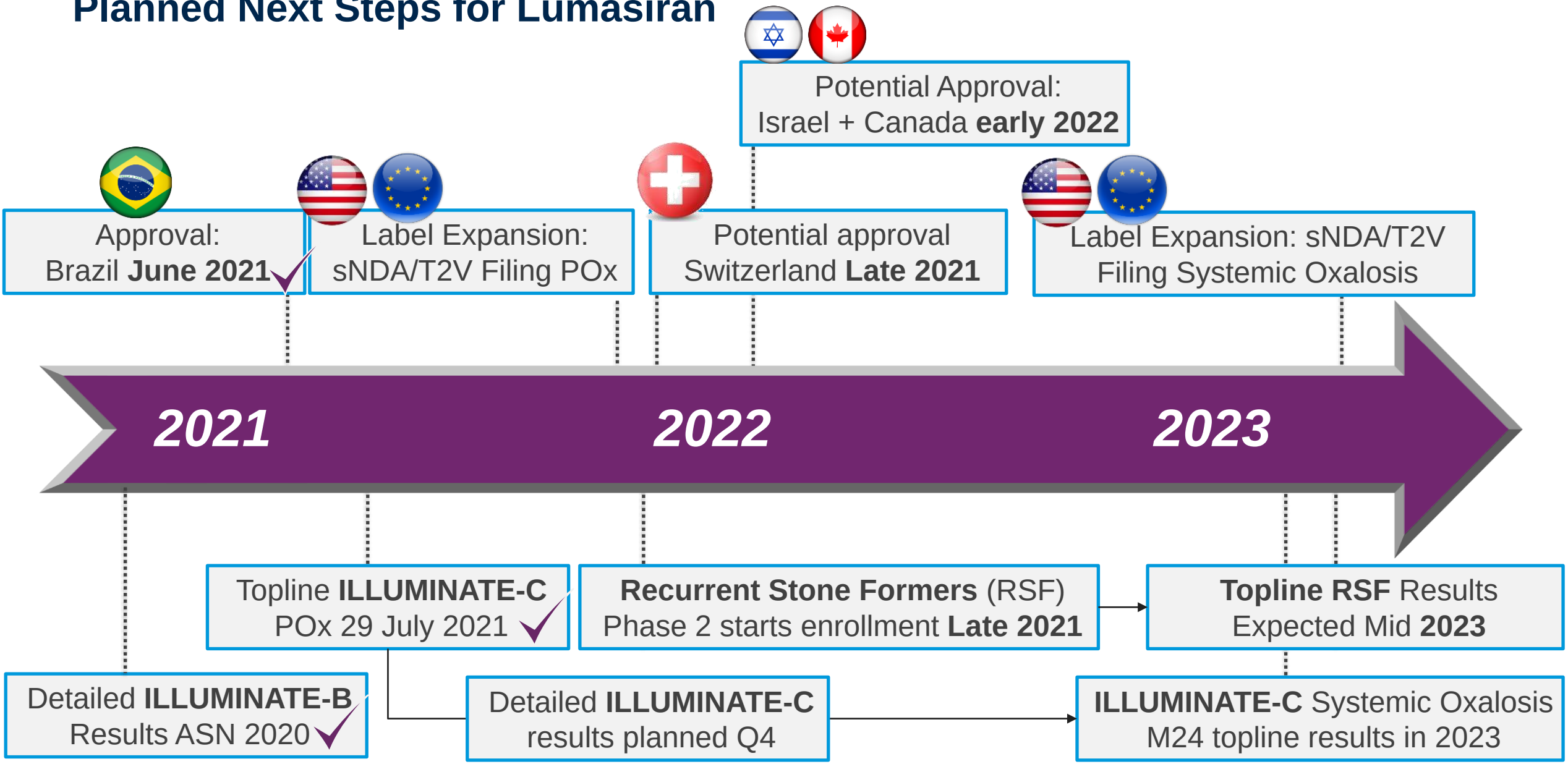
Support and Retention

Alnylam ASSIST™

Harvard Pilgrim HealthCare

Humana.

Planned Next Steps for Lumasiran



sNDA = supplemental new drug application ; T2V = Type 2 Variation ; POx = Plasma Oxalate ; NC = nephrocalcinosis

Agenda

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

Introduction
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Primary Hyperoxaluria Type 1 Burden of Disease and Diagnosis
- Jeffrey M. Saland, MD, MSCR – Professor, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Recent Highlights, Lumasiran Program: Primary Hyperoxaluria Type 1 & Recurrent Stone Formers
- John Gansner, MD, PhD – Director, Clinical Research

Lumasiran Commercial Progress PH1
- Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Q&A Session

Upcoming RNAi Roundtables

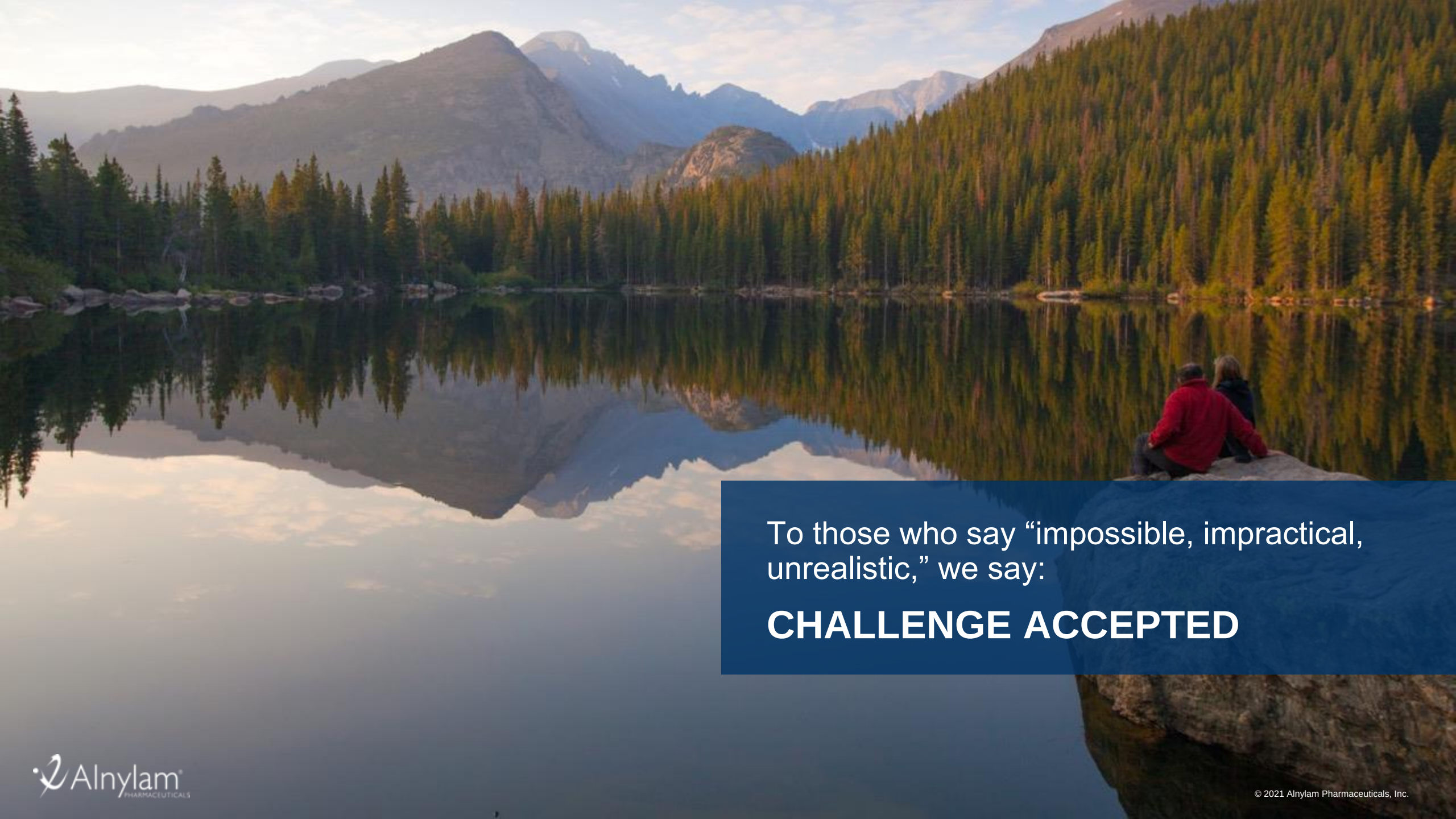
Liver-Directed RNAi Pipeline Programs

- Monday, September 20, 11:00 am ET

CNS & Extrahepatic RNAi Pipeline Programs

- Friday, October 1, 1:30 pm ET

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



Alnylam PHARMACEUTICALS