Alnylam R&D Day

New York City

December 6th, 2018

Alnylam® PHARMACEUTICALS

Agenda

Time			Topic
8:00 am	–	8:20 am	Introduction and Strategic Overview
8:20 am	–	8:35 am	New Frontiers for RNAi Therapeutics
8:35 am	–	9:20 am	ATTR Amyloidosis and TTR Program
9:20 am	–	10:00 am	Acute Hepatic Porphyria & Givosiran
10:00 am	–	10:30 am	Q&A Session 1
10:30 am	–	10:45 am	Break
10:45 am	–	11:35 am	Primary Hyperoxaluria Type 1 and Lumasiran
11:35 am	–	11:55 am	RNAi Therapeutics Platform Innovation
11:55 am	–	12:25 pm	Next Wave Programs
12:25 pm	–	12:40 pm	Q&A Session 2
12:40 pm	–	1:00 pm	Commercialization Strategy & Closing Statements

Alnylam Forward Looking Statements & Non-GAAP Financial Measures

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; successfully launching, marketing and selling its approved products globally, its 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, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

This presentation contains non-GAAP financial measures, including expenses adjusted to exclude certain non-cash expenses and non-recurring gains outside the ordinary course of the Company’s business. These measures are not in accordance with, or an alternative to, GAAP, and may be different from non-GAAP financial measures used by other companies. The items included in GAAP presentations but excluded for purposes of determining non-GAAP financial measures for the periods presented herein are stock-based compensation expense and the gain on litigation settlement. The Company has excluded the impact of stock-based compensation expense, which may fluctuate from period to period based on factors including the variability associated with performance-based grants for stock options and restricted stock units and changes in the Company’s stock price, which impacts the fair value of these awards. The Company has excluded the impact of the gain on litigation settlement because the Company believes this item is a one-time event occurring outside the ordinary course of the Company’s business.

Introduction & Strategic Overview

John Maraganore, Ph.D.

Chief Executive Officer

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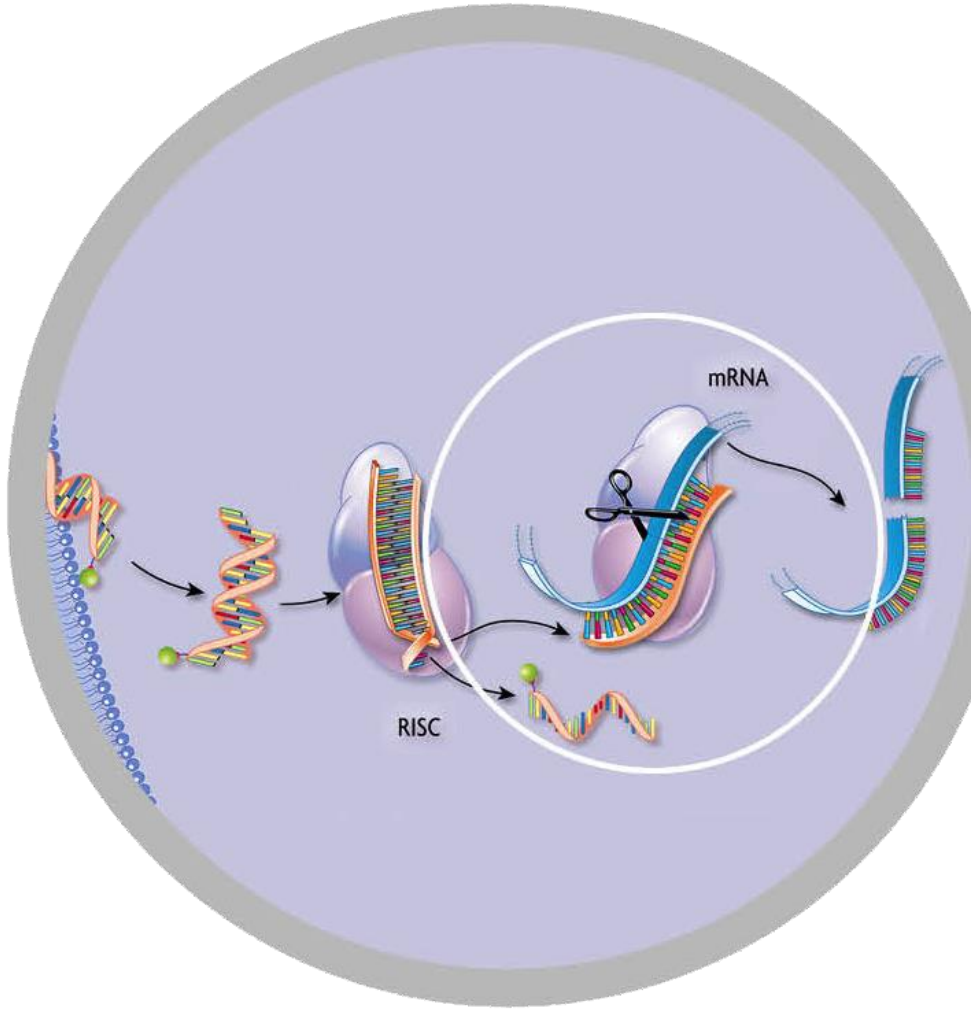
RNAi Therapeutics: New Class of Innovative Medicines

Clinically Proven Approach with Transformational Potential

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



Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

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

[1] POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2] Approved in the U.S. for the polyneuropathy of hATTR amyloidosis in adults, and in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy
[3] Includes marketing application submissions
As of December 2018

Alnylam® PHARMACEUTICALS

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- 3 STArs with Clinical Programs
- 1 Marketed Product
- 8 Clinical Programs
- 5 Late Stage Programs
- 3 Breakthrough Designations
- Substantial Global Rights

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The first RNAi therapeutic is NOW APPROVED

onpattro™
(patisiran) lipid complex injection

onpattro™
2 mg/mL concentrate for solution for infusion patisiran

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Two Horizons for Alnylam

Next 2-3 Years

- Creating a Global Commercial Company

Next 3-5 Years

- Building a Top-Tier Biotech

Alnylam 2019 Goals

*Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4

		2019*		
		Early	Mid	Late
onpattro™ (patisiran) lipid complex injection (ATTR Amyloidosis)	Commercial Execution	●	●	●
	Japan Launch			●
	Additional Country Launches	●	●	●
	Cardiomyopathy Label Expansion Plans	●		
VUTRISIRAN (ATTR Amyloidosis)	HELIOS-A Polyneuropathy Phase 3 Enrollment	●	●	●
	Start HELIOS-B Cardiomyopathy Phase 3			●
GIVOSIRAN (Acute Hepatic Porphyria)	ENVISION Phase 3 Topline Results	●		
	File NDA		●	
	File MAA		●	
LUMASIRAN (Primary Hyperoxaluria Type 1)	Complete ILLUMINATE-A Phase 3 Enrollment		●	
	ILLUMINATE-A Phase 3 Topline Results			●
	Start ILLUMINATE-B & C Phase 3 Studies		●	
ADDITIONAL CLINICAL PROGRAMS	Continue to advance early/mid-stage pipeline; File new INDs; Present clinical data	●	●	●
PARTNERED PROGRAMS				
INCLISIRAN (Hypercholesterolemia)	ORION-9, 10, & 11 Phase 3 Topline Results		●	●
	File NDA			●
FITUSIRAN (Hemophilia and RBD)	Support Sanofi on ATLAS Phase 3	●	●	●

Alnylam 2019 Goals

*Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4

		2019*		
		Early	Mid	Late
onpattro (patisiran) lipid complex injection ™ (ATT	Commercial Execution	●	●	●
	Japan Launch			●
	Additional Country Launches	●	●	●
VU (ATT				●
				●
G (Acute				
LU (Primary H				
				●
ADDITIONAL CLINICAL PROGRAMS	Continue to advance early/mid-stage pipeline; File new INDs; Present clinical data	●	●	●
PARTNERED PROGRAMS				
INCLISIRAN (Hypercholesterolemia)	ORION-9, 10, & 11 Phase 3 Topline Results		●	●
	File NDA			●
FITUSIRAN (Hemophilia and RBD)	Support Sanofi on ATLAS Phase 3	●	●	●

- Global ONPATTRO Launch
- 5 Phase 3 Programs Ongoing
- 3 Phase 3 Program Readouts
- 2 NDA Filings

Goal to Bring Innovation to Patients and Markets Around World

2018	2019-2021			Partnered programs*: 2020-2021	
onpattro® (patisiran) lipid complex injection	**Givosiran**	**Lumasiran**	**Vutrisiran**	**Fitusiran**	**Inclisiran**
ONPATTRO is indicated in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults^	Acute hepatic porphyria	Primary hyperoxaluria type 1	ATTR amyloidosis	Hemophilia	Hypercholesterolemia

* Sanofi Genzyme is leading and funding development of fitusiran and will commercialize program, if successful;
The Medicines Company is leading and funding development of inclisiran and will commercialize program, if successful
^ ONPATTRO is approved in the EU for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy
Anticipated dates of launch based on current development timelines and assuming regulatory approval

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Alnylam®
PHARMACEUTICALS
2020
3 STArs
3 Marketed Products
10 Clinical Programs
4 Late Stage Programs

Two Horizons for Alnylam

Next 2-3 Years

- Creating a Global Commercial Company

Next 3-5 Years

- Building a Top-Tier Biotech

Building a Top-Tier Biotech

Potential for Significant Transformation of Alnylam over Next 5 Years

2018

1	Approved Products
5	Late Stage Programs
3	STArs
	Largely U.S.
~1K	Employees
	CMOs

2023

5+	Approved Products
10+	Late Stage Programs
4+	STArs
	Global
~2.5K	Employees
	Norton + CMOs

Top 5 independent, global biopharma company admired for its dedication to **patients**, corporate **culture**, scientific **innovation**, social **responsibility**, and commercial **excellence** with numerous RNAi products across orphan and large disease areas

Building a Top-Tier Biotech

Potential for Significant Transformation of Alnylam over Next 5 Years

Biogen 1995 – 2001

GILEAD 2000 – 2006^

REGENERON 2007 – 2013

VERTEX 2010 – 2016

1 year prior → 5 years post launch	Pipeline Density Change[2]	Launched Drugs During Timeframe	Change in Market Cap[3]
Analogue average[1]	~1.4	~3 *~50% partnered*	~21.0B
Alnylam forecasts	~4.6	5+ *~30% partnered*	TBD

[1] LEK Research
[2] Pipeline density is measure of aggregate likelihood of success of each companies' pipeline, calculated based on phase of asset's lead indication
[3] Financials adjusted for yearly inflation to present value in 2018
^ Gilead analysis excluded Vistide launch in 1996 (CMV retinitis for AIDS patients) given out-licensing deals (Pharmacia & Upjohn)

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Building a New Class of Medicines

Significant Opportunity to Pioneer over Next 5 Years

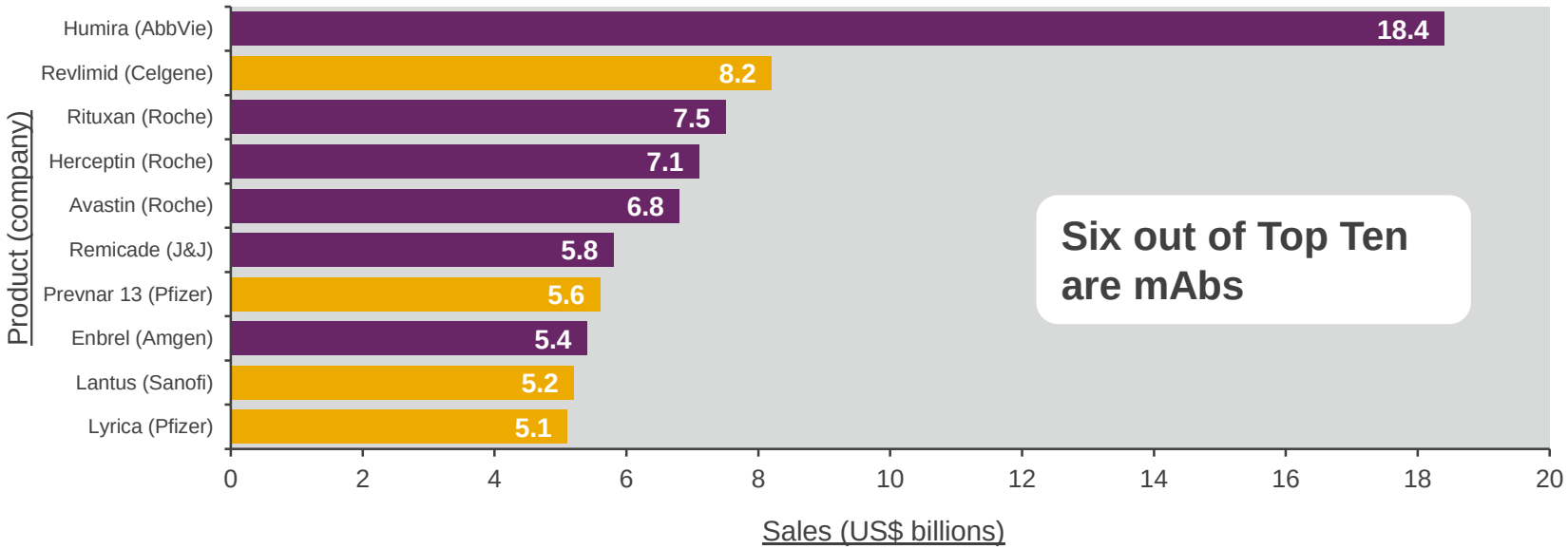
mAb Therapeutics

Discovery by Kohler & Milstein *Nature* 256: 495	Nobel Prize in Physiology or Medicine to Jerne, Kohler & Milstein	ReoPro – first approved drug to market
1975 →	**1984** →	**1994**
9 years	*10 years*	

RNAi Therapeutics

Discovery by Fire & Mello *Nature* 391: 806	Nobel Prize in Physiology or Medicine to Fire & Mello	ONPATTRO – first RNAi based drug approved
1998 →	**2006** →	**2018**
8 years	*12 years*	

Top drugs in 2017*



Six out of Top Ten are mAbs

* Nature Reviews Drug Discovery, 17. 232 (2018)

New Frontiers for RNAi Therapeutics

Akshay Vaishnaw, M.D., Ph.D.

President, Research & Development

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RNAi Therapeutics: New Class of Innovative Medicines

Clinically Proven Approach with Transformational Potential

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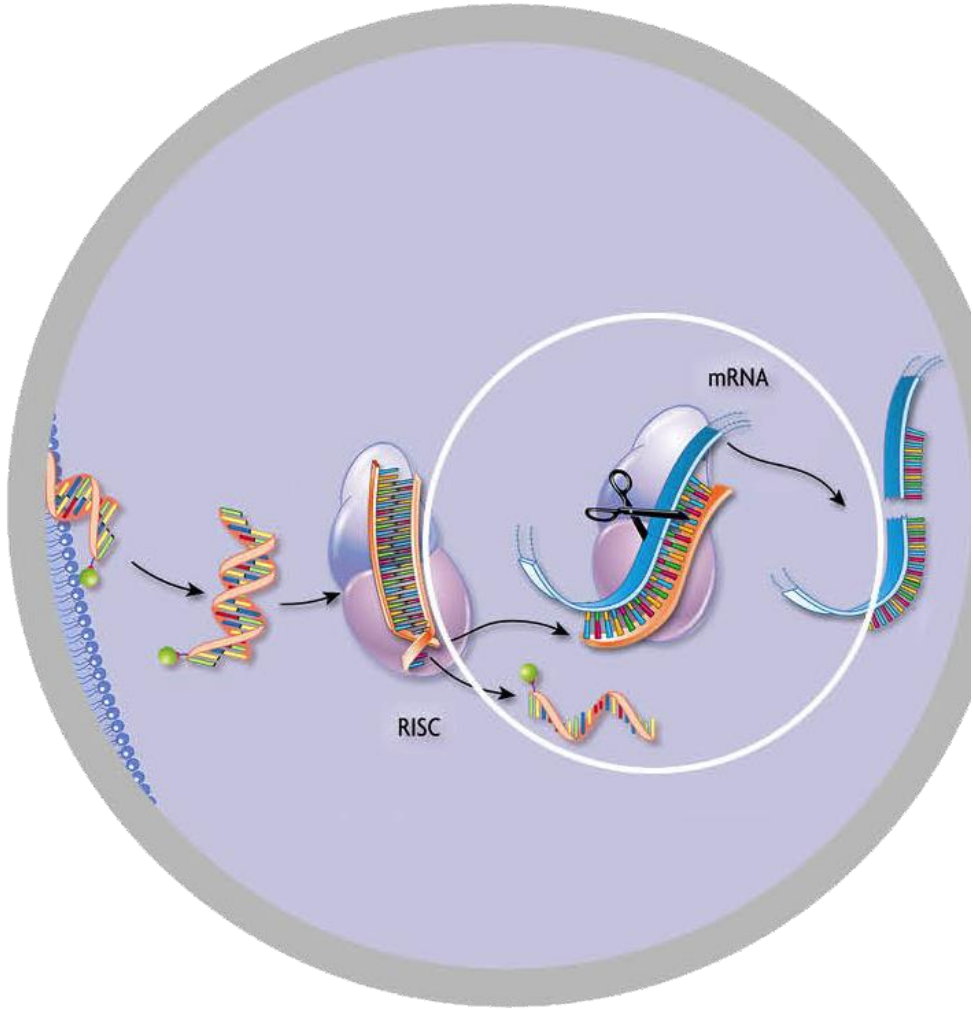
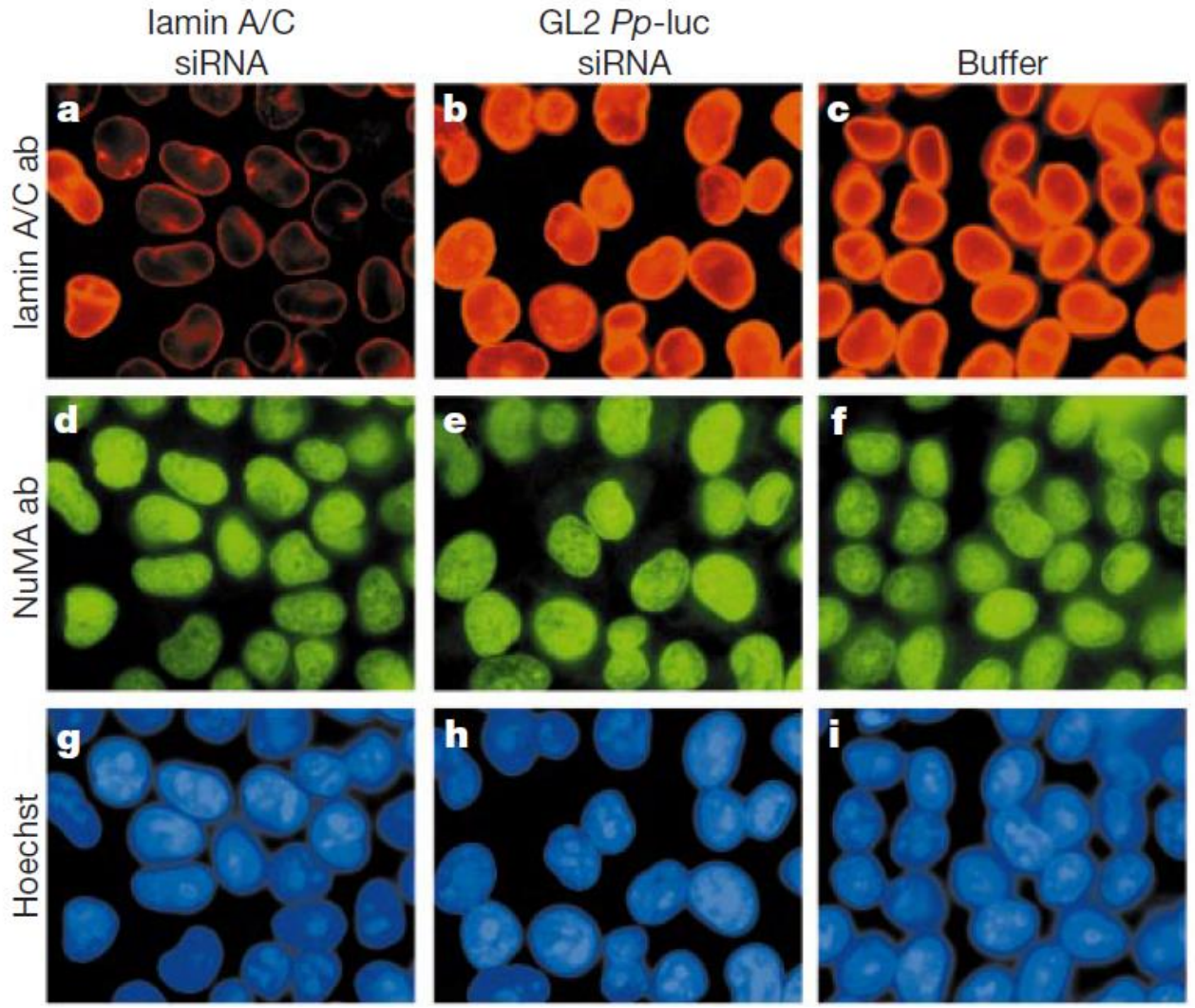


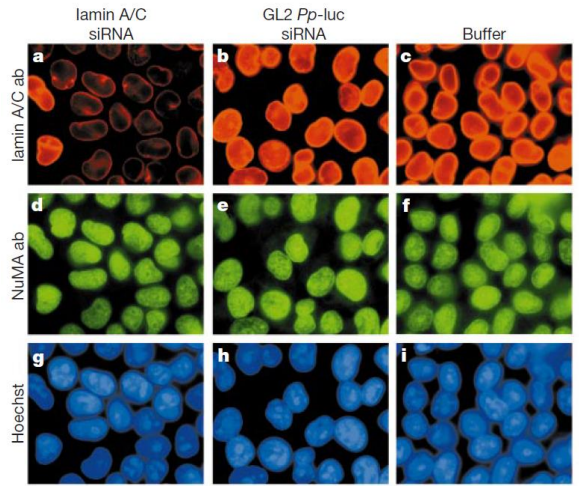
In Vitro Data that Started Alnylam

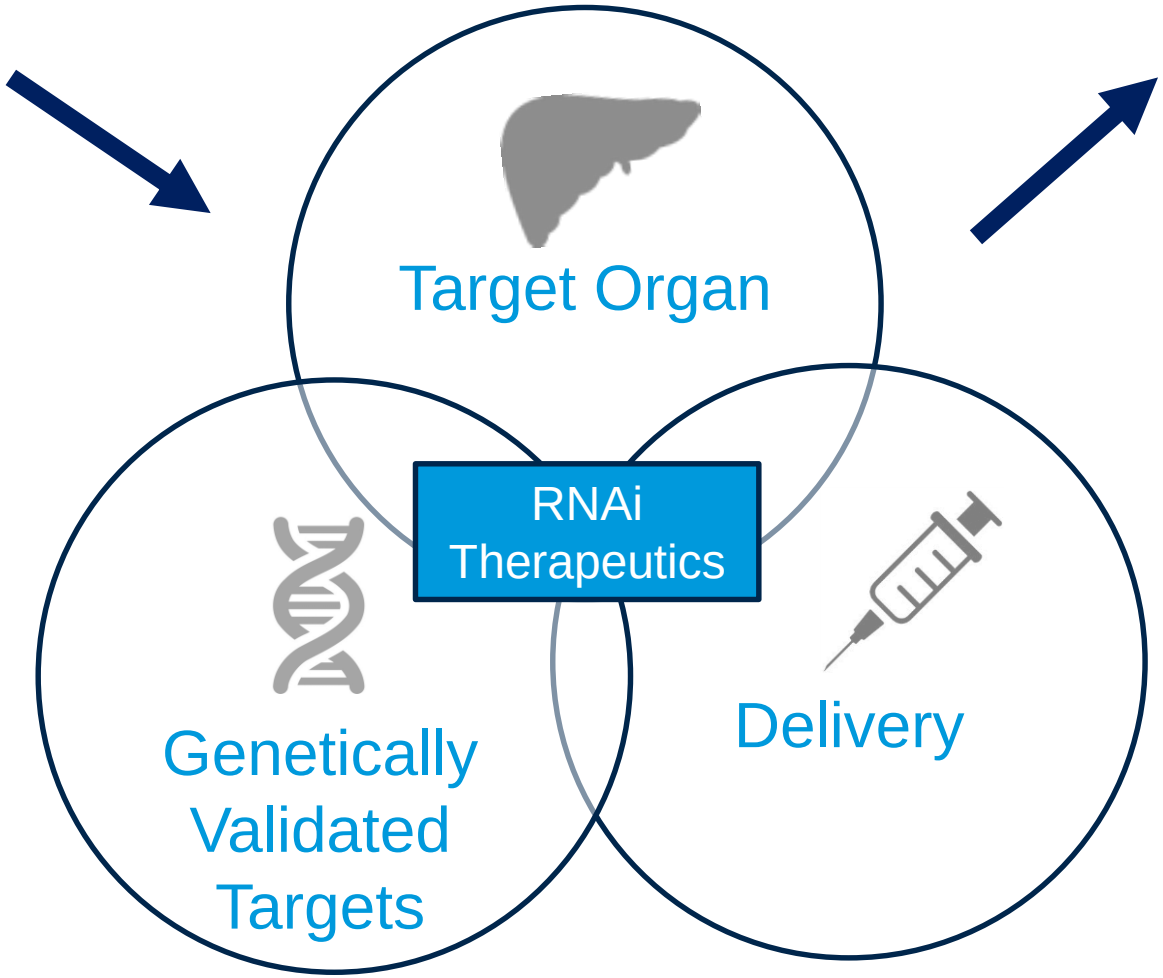
Elbashir et al., Nature, 2001;411:494-98

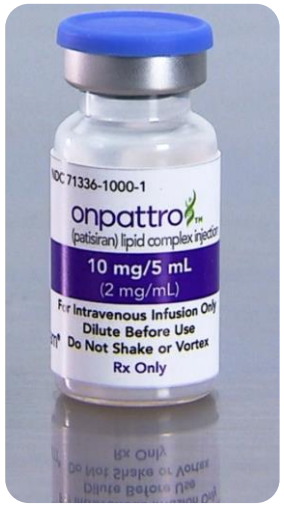


Focused R&D Strategy

Turning an *InVitro* Observation into a New Class of Medicines

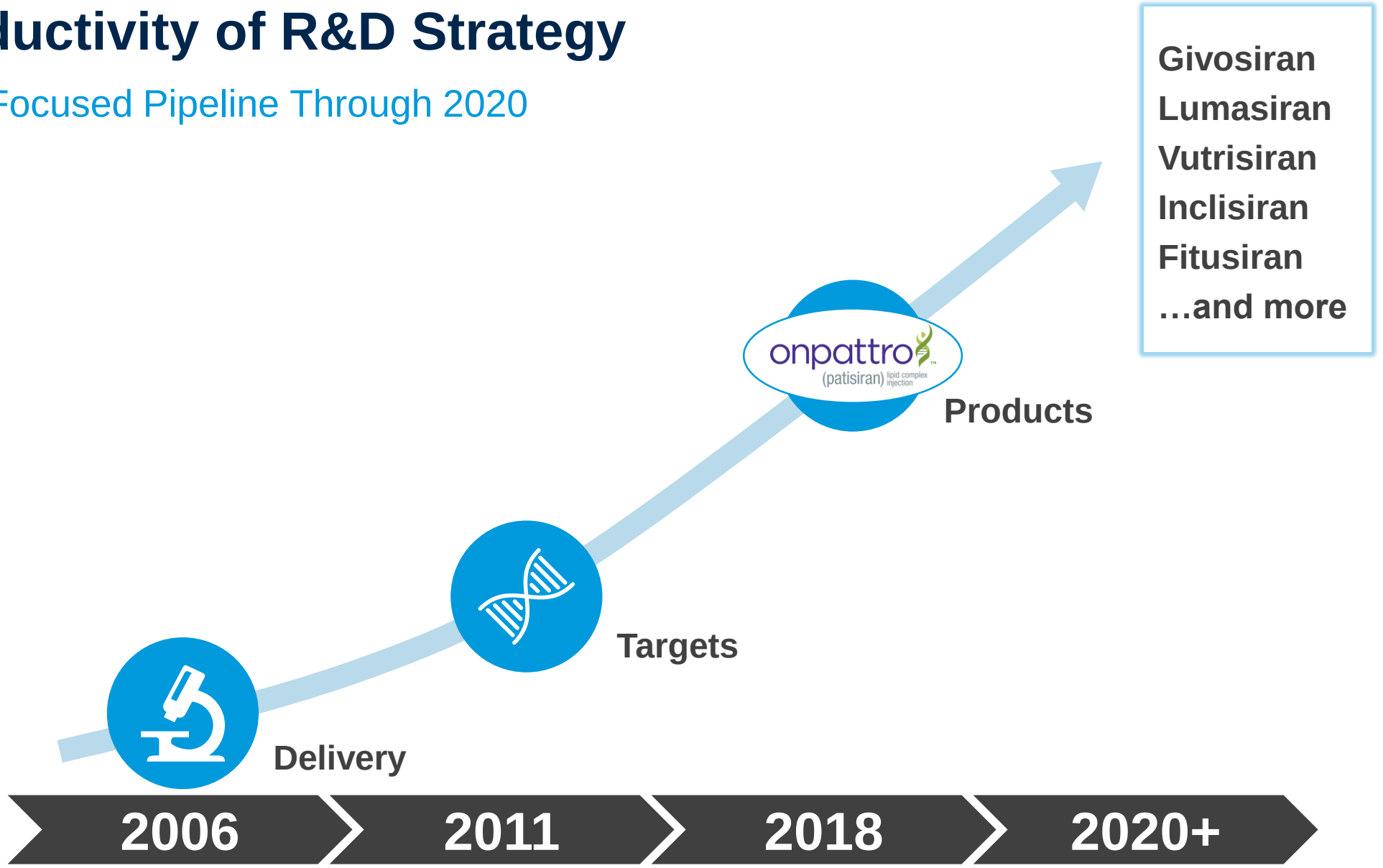






Productivity of R&D Strategy

Liver-Focused Pipeline Through 2020



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Productivity of R&D Strategy

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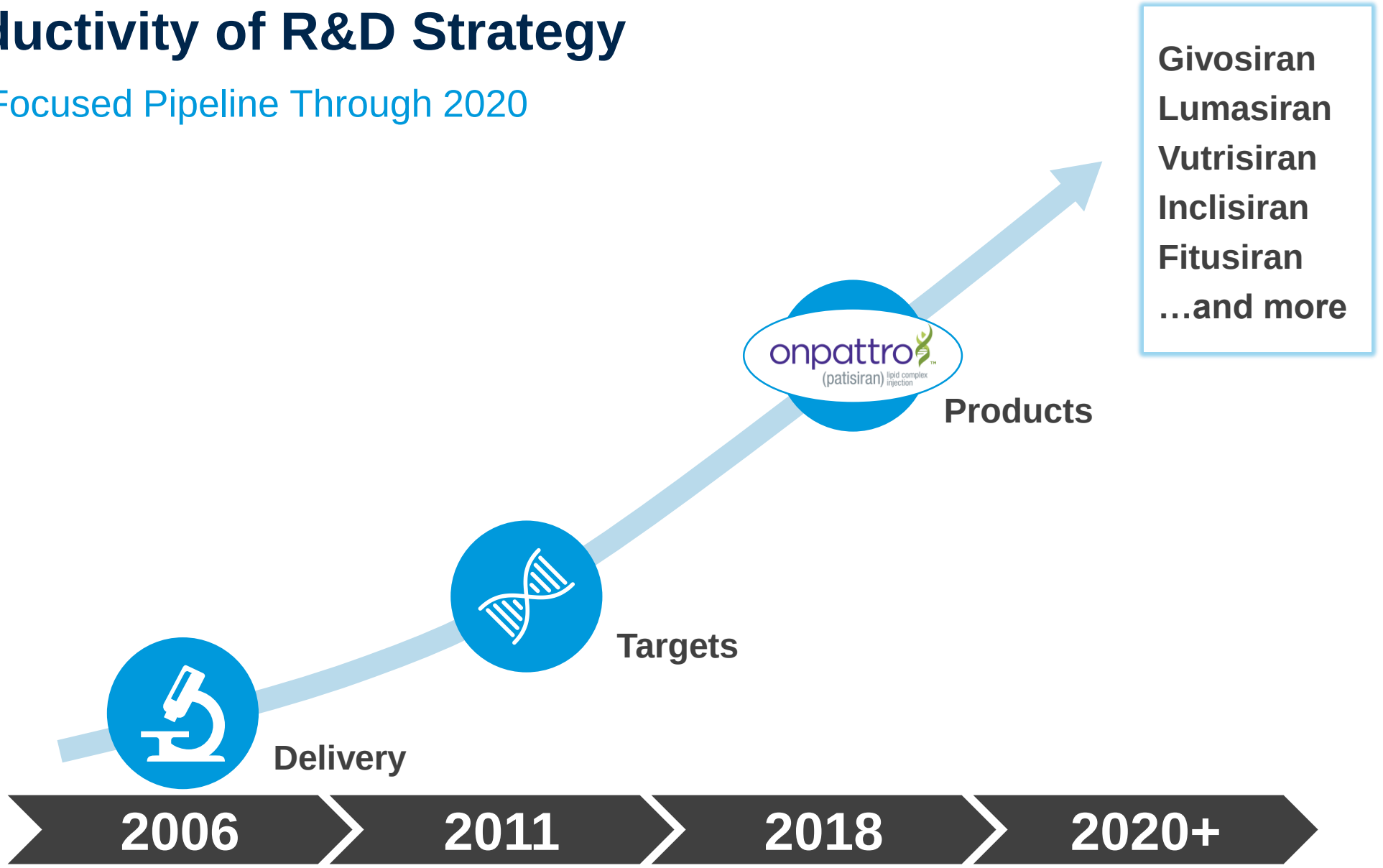


Expand Opportunity for Existing Liver Programs

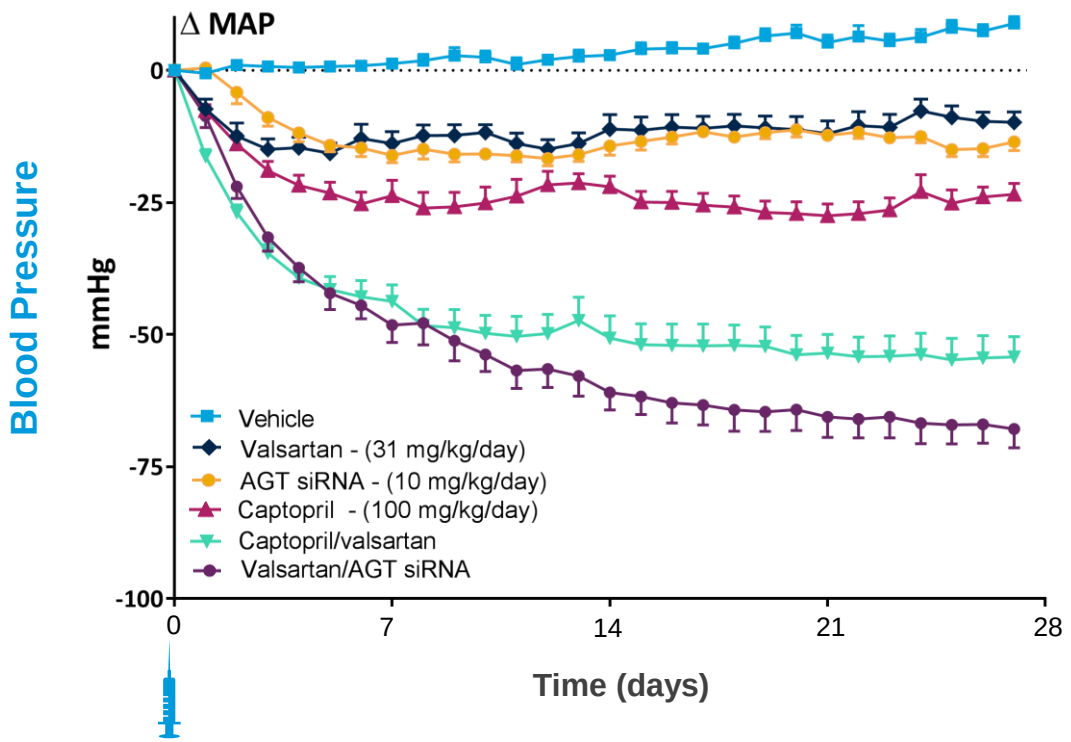
Invest in Product Lifecycles

		Expansion Opportunity
ONPATTRO Vutrisiran *hATTR amyloidosis polyneuropathy*		**All ATTR Amyloidosis**
Givosiran *AHP recurrent attacks*		**Sporadic AHP Attacks and Chronic Manifestations**
Lumasiran *Primary Hyperoxaluria Type I*		**Idiopathic Stone Formation**

Expanding Liver R&D Strategy

Continue to Harvest Liver R&D Opportunities

E.g., ALN-AGT in Rat Hypertension Model



Highly Productive Discovery Engine

Next Wave Opportunities:

ALN-AAT02
Alpha-1 Antitrypsin Deficiency Liver Disease

ALN-HBV02
(VIR-2218)
Chronic HBV Infection

ALN-LEC
LECT2 Amyloidosis

ALN-AGT
Hypertension

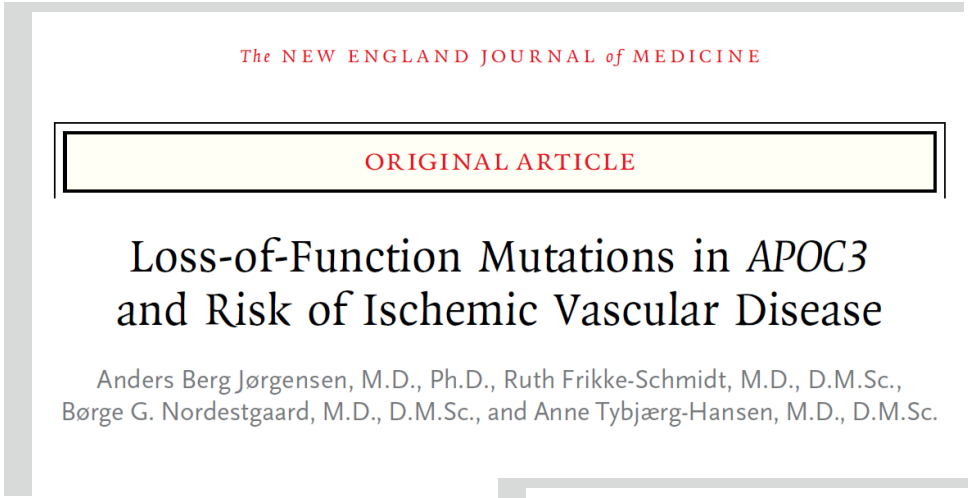
ALN-F12
Thromboembolism

ALN-HSD
Nonalcoholic Steatohepatitis (NASH)

Many other undisclosed opportunities…..

Expanding Liver R&D Strategy

Access New Genetically Validated Targets, Recent Examples

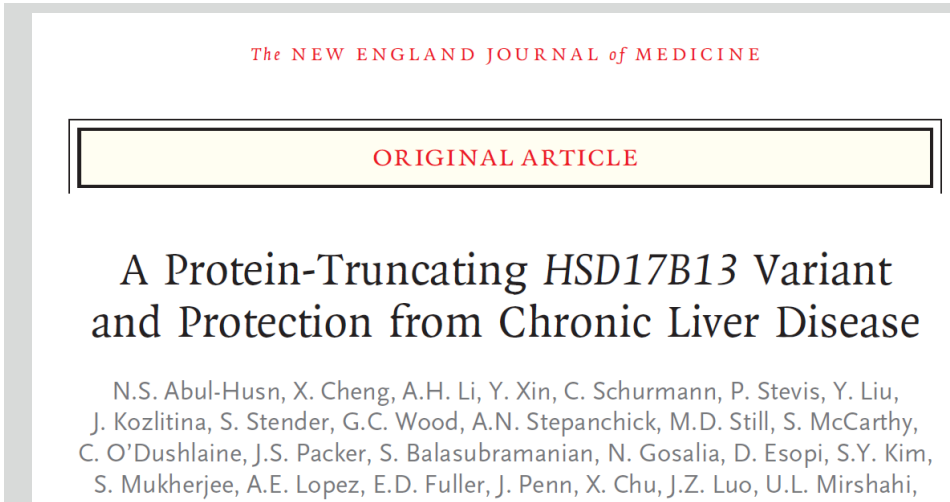


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc., Børge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.

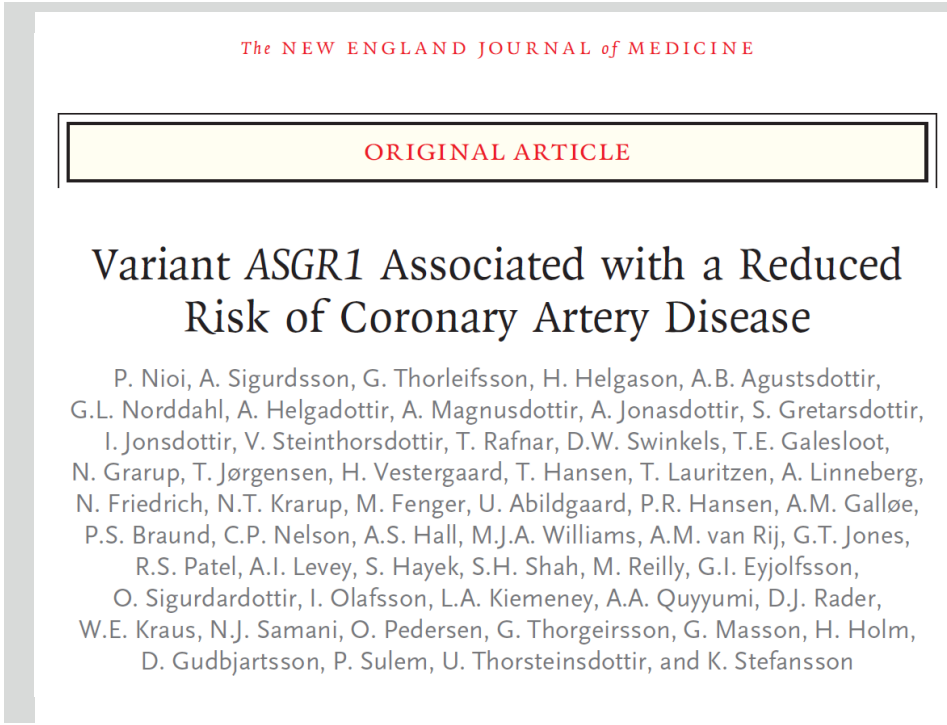


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Protein-Truncating *HSD17B13* Variant and Protection from Chronic Liver Disease

N.S. Abul-Husn, X. Cheng, A.H. Li, Y. Xin, C. Schurmann, P. Stevis, Y. Liu, J. Kozlitina, S. Stender, G.C. Wood, A.N. Stepanchick, M.D. Still, S. McCarthy, C. O'Dushlaine, J.S. Packer, S. Balasubramanian, N. Gosalia, D. Esopi, S.Y. Kim, S. Mukherjee, A.E. Lopez, E.D. Fuller, J. Penn, X. Chu, J.Z. Luo, U.L. Mirshahi, D.J. Carey, C.D. Still, M.D. Feldman, A. Small, S.M. Damrauer, D.J. Rader, B. Zambrowicz, W. Olson, A.J. Murphy, I.B. Borecki, A.R. Shuldiner, J.G. Reid, J.D. Overton, G.D. Yancopoulos, H.H. Hobbs, J.C. Cohen, O. Gottesman, T.M. Teslovich, A. Baras, T. Mirshahi, J. Gromada, and F.E. Dewey



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Variant *ASGR1* Associated with a Reduced Risk of Coronary Artery Disease

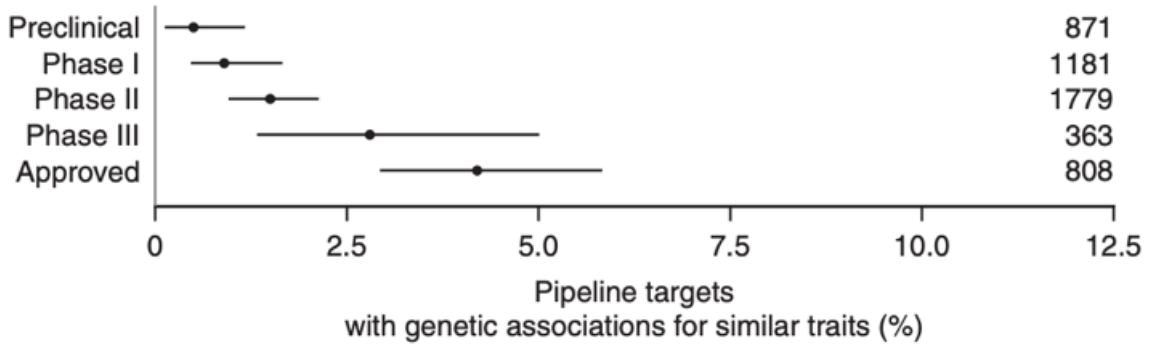
P. Nioi, A. Sigurdsson, G. Thorleifsson, H. Helgason, A.B. Agustsdottir, G.L. Norddahl, A. Helgadottir, A. Magnusdottir, A. Jonasdottir, S. Gretarsdottir, I. Jonsdottir, V. Steinthorsdottir, T. Rafnar, D.W. Swinkels, T.E. Galesloot, N. Grarup, T. Jørgensen, H. Vestergaard, T. Hansen, T. Lauritzen, A. Linneberg, N. Friedrich, N.T. Krarup, M. Fenger, U. Abildgaard, P.R. Hansen, A.M. Galløe, P.S. Braund, C.P. Nelson, A.S. Hall, M.J.A. Williams, A.M. van Rij, G.T. Jones, R.S. Patel, A.I. Levey, S. Hayek, S.H. Shah, M. Reilly, G.I. Eyjolfsson, O. Sigurdardottir, I. Olafsson, L.A. Kiemeney, A.A. Quyyumi, D.J. Rader, W.E. Kraus, N.J. Samani, O. Pedersen, G. Thorgeirsson, G. Masson, H. Holm, D. Gudbjartsson, P. Sulem, U. Thorsteinsdottir, and K. Stefansson

Alnylam PHARMACEUTICALS

Genetically Validated Targets More Likely to Succeed

Medicines are 2x more likely to be approved if target is genetically validated

Progression	*p*(progress|genetics)/ *p*(progress|no genetics)
Phase I to phase II	1.2 (1.1–1.3)
Phase II to phase III	1.5 (1.3–1.7)
Phase III to approval	1.1 (1.0–1.2)
Phase I to phase III	1.8 (1.5–2.1)
Phase I to approval	2.0 (1.6–2.4)



Nelson et al., Nat Gen. 2015,47:856-60.

UK Biobank Consortium

World-leading effort to connect genotype to full medical records for phenome-wide association studies

- Goal to generate 500K exome sequences linked to medical records by end-2019
  - 50K exomes sequenced to date

Contributions to Liver R&D Strategy

- Access new targets
  - ~800 genes with homozygous or compound heterozygous loss-of-function (human KO) observed in at least 1 individual
- Interrogate database
  - New insights on patients with hATTR mutations
    - Features at disease onset?
    - Predictors of disease penetrance
  - Prevalence of AHP mutations
    - Identify patients
    - Define morbidity in patients with PBGD mutations without AIP diagnosis
  - Identify patients with AGXT mutations without PH1 diagnosis

UK Biobank Case Study

E.g., V122I Mutation Associated with hATTR Amyloidosis

Preliminary data from V122I positive individuals in UKBB database

- 384 individuals identified
- Opportunity to understand pre-diagnostic features, spectrum of manifestations and effect of V122I homozygosity

ICD10 code	V122I Count	V122I prevalence	Disease	UKBB count	UKBB prevalence
G560	18	0.04712	Carpal tunnel syndrome	11350	0.02894
G589	1	0.00262	Mononeuropathy, unspecified	99	0.00025
G628	1	0.00262	Other specified polyneuropathies	156	0.00040
G629	5	0.01309	Polyneuropathy, unspecified	311	0.00079
G632	1	0.00262	Diabetic polyneuropathy	3	0.00001
E854	1	0.00262	Organ-limited amyloidosis	39	0.00010
I500	6	0.01571	Congestive heart failure	1023	0.00261
I501	4	0.01047	Left ventricular failure	862	0.00220
I509	2	0.00524	Heart failure, unspecified	372	0.00095

Only 1 diagnosis of amyloidosis amongst the entire cohort
26/384 V122I carriers show at least one of these symptoms

RNAi Therapeutics: Extensive Human Safety Experience

Encouraging Profile to Date

Number of Programs	Number of Clinical Studies	Total Patients or Volunteers Dosed	Greatest Duration of Exposure
>15	>36	>3500	>60 months

Minimal platform related findings*

- Low incidence (~3%) of generally mild, asymptomatic, reversible LFT increases >3x ULN
- Injection site reactions (~20%) generally mild, transient and rarely led to discontinuation
  - No events of ulceration, necrosis or tissue damage
- One report of anaphylaxis (<0.05%) in patient with prior history of atopy**
- No evidence of broader platform implications from revusiran program discontinuation in 2016
  - Revusiran employed earlier generation STC platform and 12-280x higher doses

Favorable emerging profile for ESC-GalNAc platform compared with competing oligo platforms†

- No evidence of thrombocytopenia, renal toxicity, or systemic inflammatory effects

*Experience as of October 2018 – Data estimated based on available safety data
**Givosiran OLE study, reported April 2018
† Not based on direct comparative studies

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Growing Safety Database Supports Expansion to Large Indications

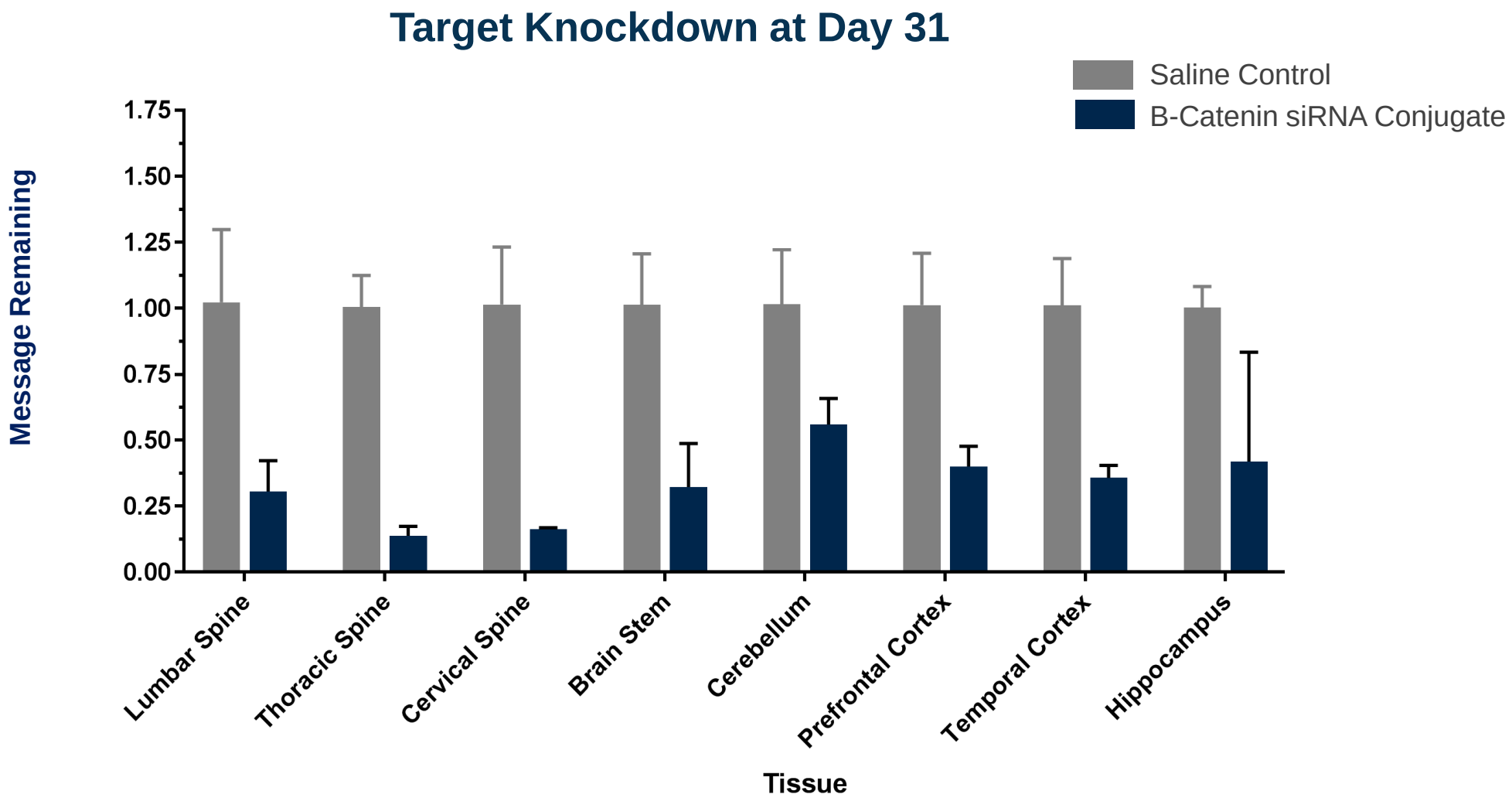
Genetic Medicines

Hepatic Infectious Diseases, CV/Metabolic Disorders

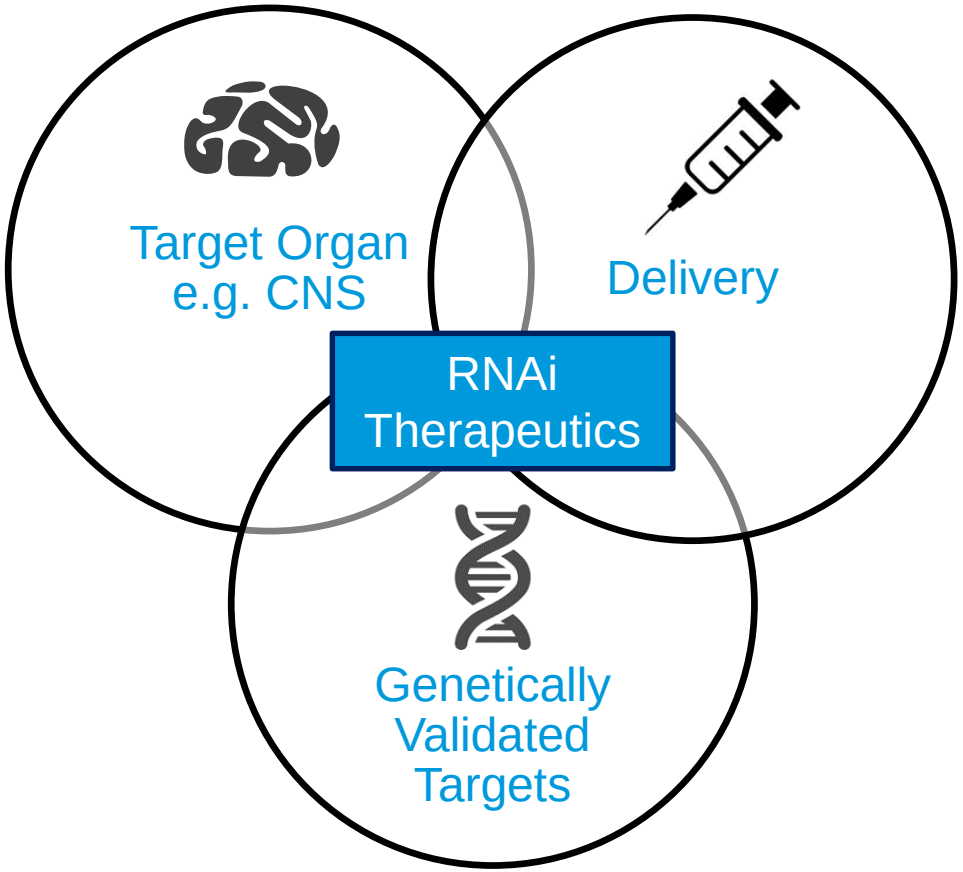
* Intended to be illustrative and not intended to represent specific estimates of patient numbers

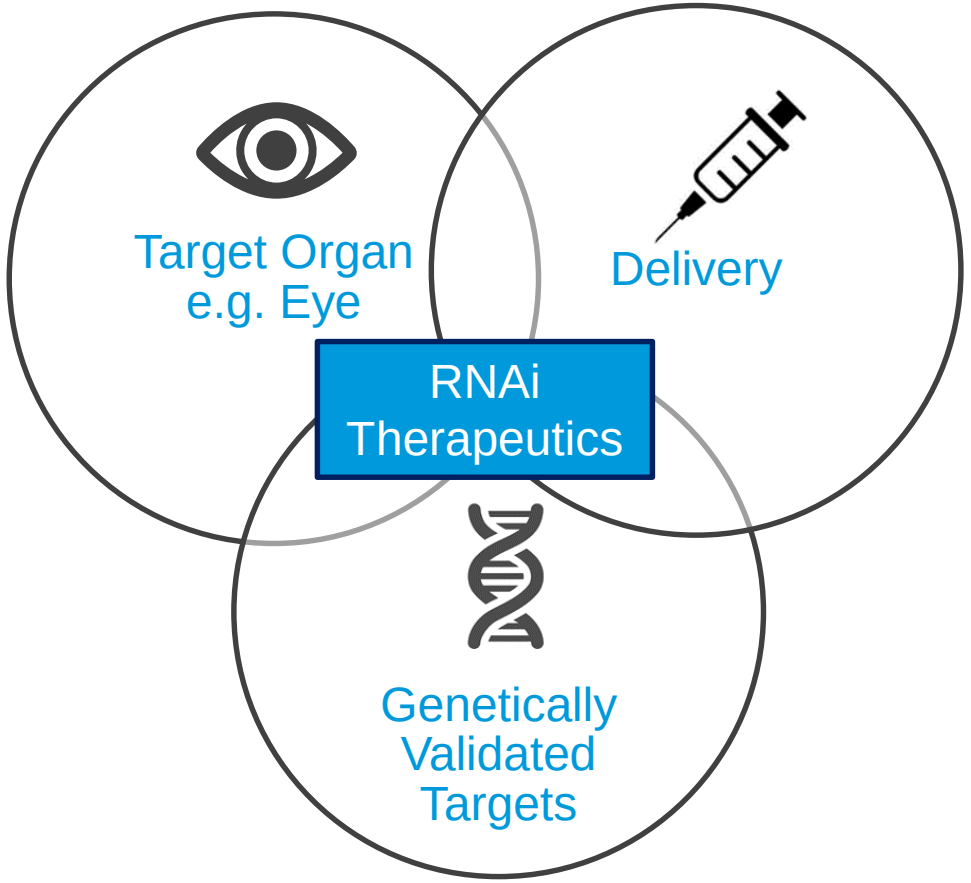
Robust, Durable, and Widespread CNS Delivery of RNAi Therapeutics

Major Breakthrough Expanding RNAi Therapeutics Opportunity



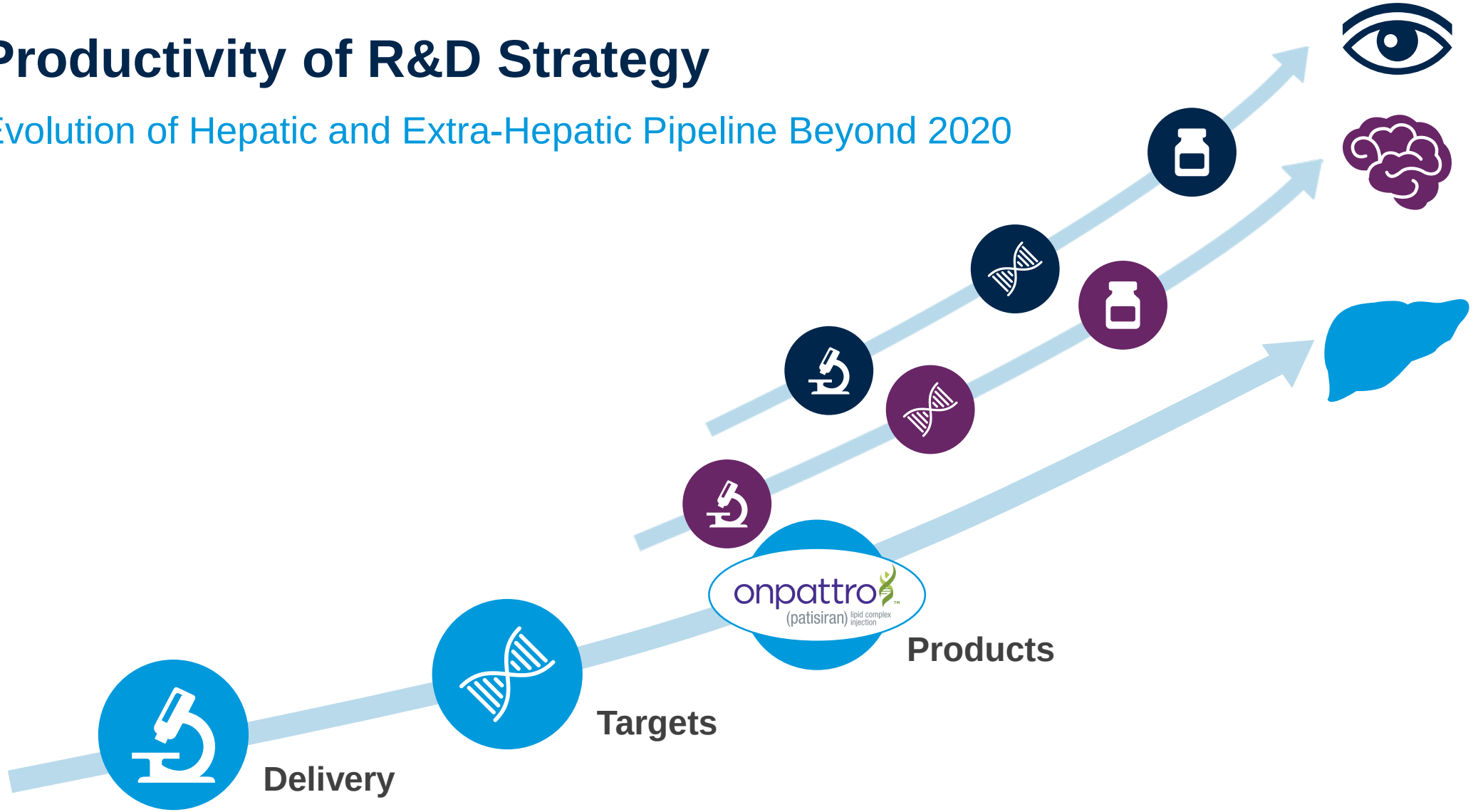
Use Liver Learnings to Build Pipeline for Other Organs



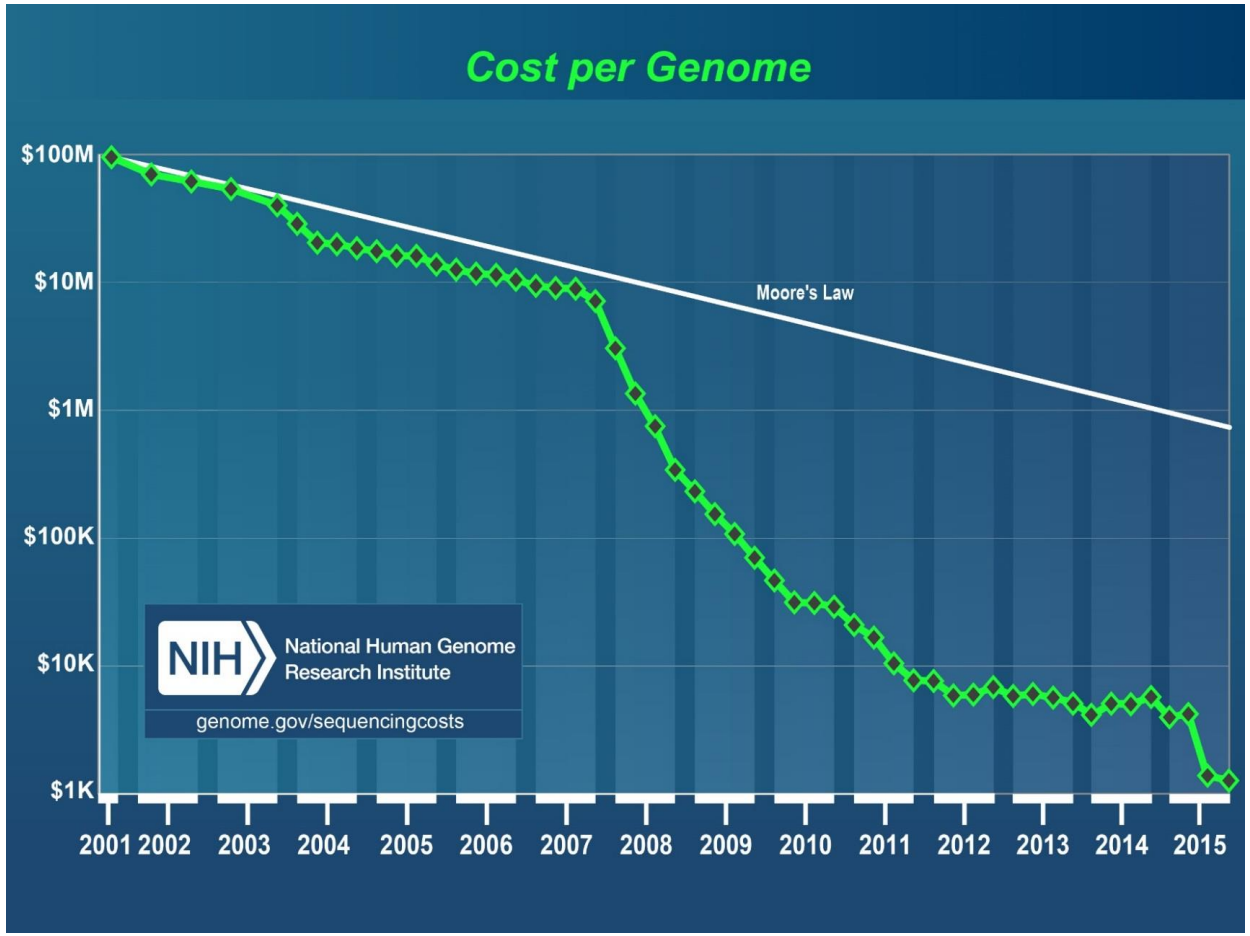


Productivity of R&D Strategy

Evolution of Hepatic and Extra-Hepatic Pipeline Beyond 2020



Advances in Genetics Will Drive Future Opportunities



- Cost to generate whole human genome sequence by late in 2015 was ~$1500
  - Rapidly approaching ~$100/genome
- Number of pathogenic allelic variants
  - 2006 → 1,822 genes
  - 2017 → 3,275 genes
  - 2027 → >>3,275 genes
- Ability to identify root causes of debilitating genetic diseases creates significant opportunity for RNAi therapeutics

Transthyretin (TTR) Amyloidosis

Eric Green, VP & General Manager, TTR Program

Pushkal Garg, M.D., Chief Medical Officer

Andy Orth, SVP, Head of U.S. Business

Alnylam® PHARMACEUTICALS

The first RNAi therapeutic is NOW APPROVED

onpattro™
(patisiran) lipid complex injection

onpattro™
2 mg/mL concentrate for solution for infusion patisiran

Alnylam® PHARMACEUTICALS

Transthyretin (TTR) Amyloidosis Program

ONPATTRO™ (patisiran) & Vutrisiran (ALN-TTRsc02)

R&D Update

- APOLLO results as basis for U.S. and EU labels
- ONPATTRO label expansion opportunity
- Vutrisiran ("*voo-TREE-si-ran*")*

Commercial Update

- United States
- EU and Canada
- Japan

* Investigational

Kipper
Living with hATTR Amyloidosis

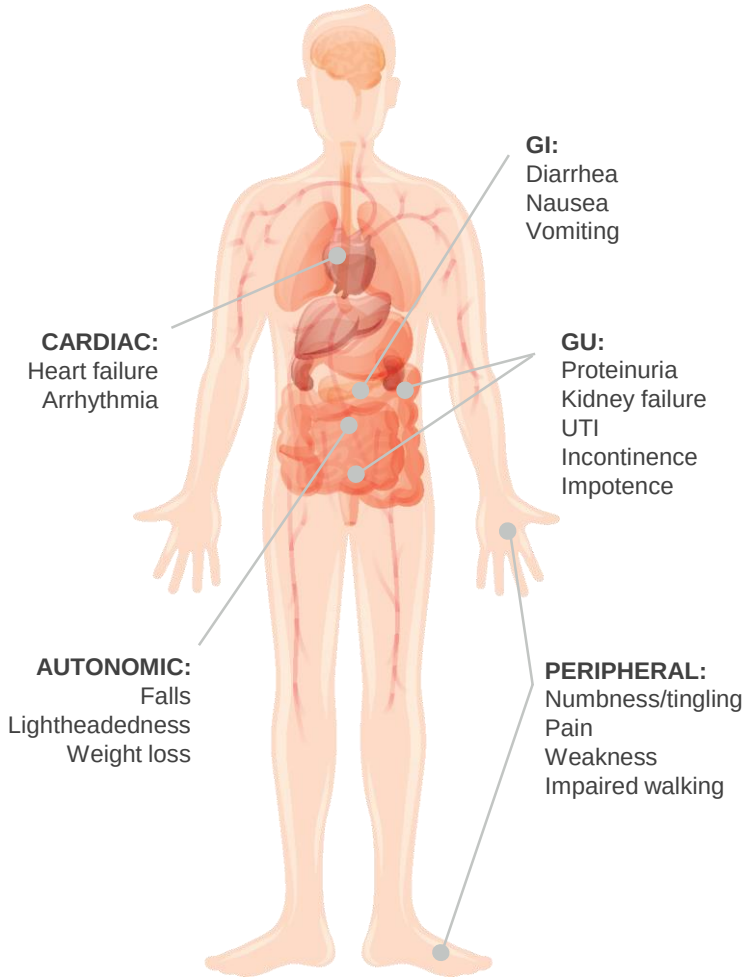
ATTR Amyloidosis

Rare, Progressively Debilitating, and Often Fatal Disease

Caused by misfolded TTR protein that accumulate as amyloid deposits in multiple tissues including heart, nerves, and GI tract

Two forms of disease:

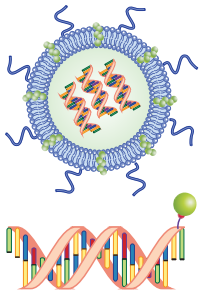
- Hereditary ATTR (hATTR) amyloidosis
  - **~50,000 patients worldwide**
  - Inherited in autosomal dominant manner
  - Multi-systemic disease including polyneuropathy, cardiomyopathy or mixed phenotype
  - Median survival 4.7 years from diagnosis
- Wild-type ATTR (wtATTR) amyloidosis
  - **~200,000 – 300,000 patients worldwide**
  - Spontaneously occurring
  - Predominantly includes cardiomyopathy, leading to heart failure



[1] Coelho T, et al. N Engl J Med. 2013;369(9):819-829
* Ando et al., Orphanet J Rare Dis, 2013; Ruberg et al., Circulation, 2012

RNAi Mechanism Addresses Fundamental Cause of ATTR Amyloidosis

Production of mutant and wild type TTR



Unstable circulating TTR tetramers ***reduced***

Organ deposition of monomers, amyloid (β-pleated) fibril ***prevented***, ***clearance promoted***

Disease manifestation ***stabilization or improvement***

RNAi Therapeutic Hypothesis

Patisiran and vutrisiran act to knock down both mutant and wild type TTR production

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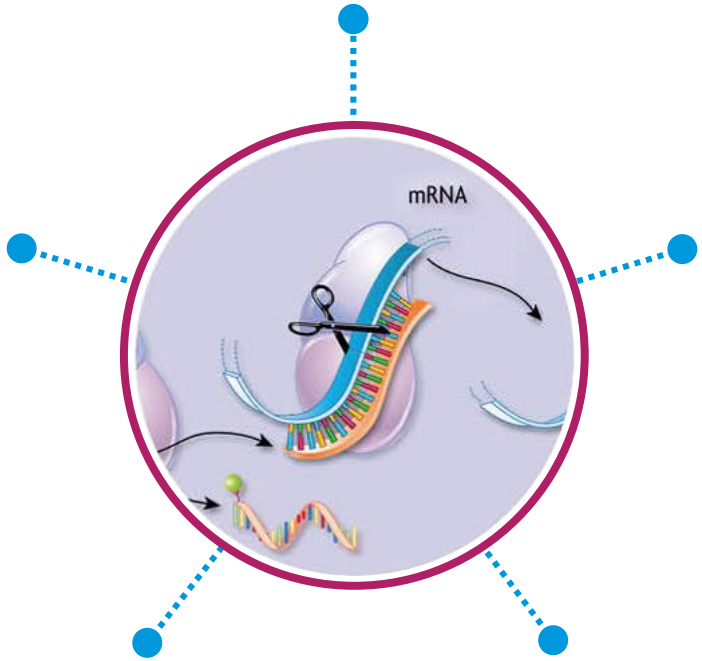
Potential Best-in-Class Approach for ATTR Amyloidosis

Potential to address both hereditary (all mutations) and wild-type disease

Potential to halt and even reverse disease manifestations



Address multi-systemic manifestations of liver-derived TTR production:

- Neuropathy
- Cardiac
- Gastrointestinal
- Autonomic

Potential to address ocular and CNS manifestations of disease with recent platform advances

Two therapies in development:

- ONPATTRO: approved* in U.S. and EU (IV q3w)
- Vutrisiran: in Phase 3 development (SQ q3m)

* ONPATTRO is approved in the U.S. for the treatment of the polyneuropathy of hATTR amyloidosis in adults, and in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy

APOLLO Phase 3 Study Design

Randomized, Double-Blind, Placebo-Controlled Study in hATTR Amyloidosis Patients with Polyneuropathy

Patient Population

- hATTR amyloidosis: any TTR mutation, FAP Stage 1 or 2
- Neuropathy impairment score (NIS) of 5-130
- Includes patients with NYHA Class 1 or 2 cardiac disease

ClinicalTrials.gov Identifier: NCT01960348

2:1 RANDOMIZATION

Patisiran 0.3 mg/kg IV q3W*

or

Placebo IV q3W*

Primary Endpoint

- Change in mNIS+7 from baseline at 18 months

Secondary Endpoints

- Norfolk QOL-DN
- NIS-weakness
- Activities of daily living (R-ODS)
- 10-meter walk
- mBMI
- Autonomic function (COMPASS-31)

Select Exploratory Endpoints

- EQ-5D QOL
- NIS+7
- Serum TTR levels
- Cardiac assessments
- Grip strength
- Skin biopsies for nerve fiber density and amyloid

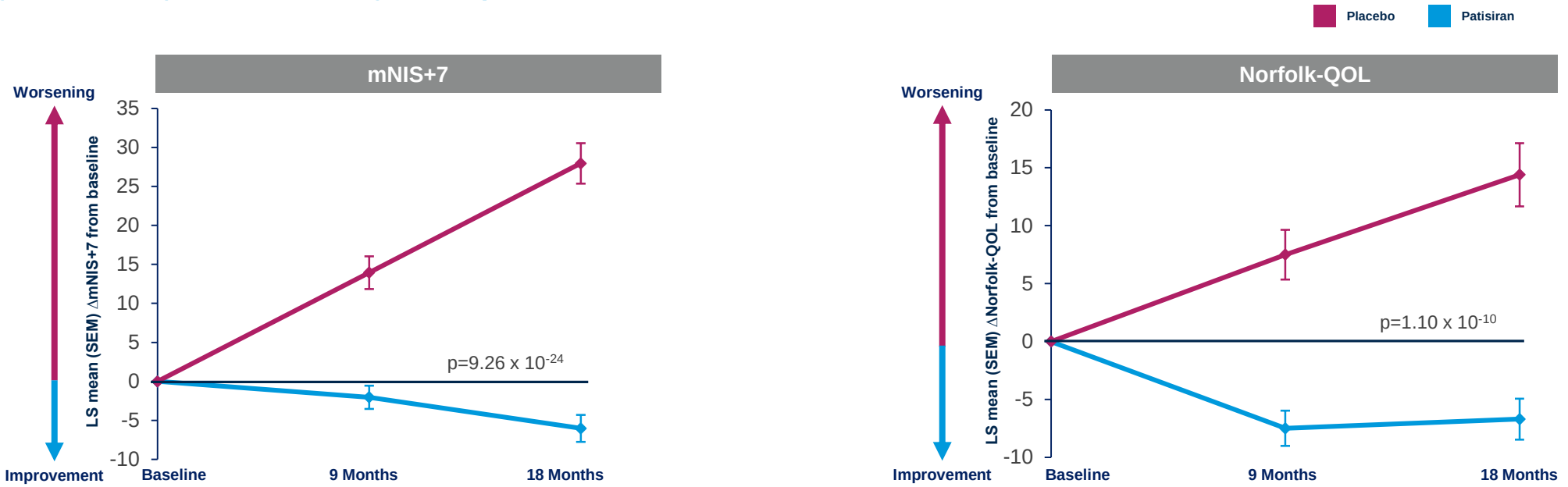
*To reduce likelihood of infusion-related reactions, patients received following premedication or equivalent at least 60 min before each study drug infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers.

99% of patients who completed APOLLO study enrolled in Global OLE study

OLE, open-label extension; ClinicalTrials.gov Identifier: NCT02510261
Adams D, et al. BMC Neurology 2017

APOLLO Phase 3 Study Results

Primary and Key Secondary Endpoints Met



At 18 months

- -6.0 point change relative to baseline
- 34.0 point difference relative to placebo
- 56.1% of patients improved*

At 18 months

- -6.7 point change relative to baseline
- 21.1 point difference relative to placebo
- 51.4% of patients improved*

All secondary endpoints encompassing QOL, walk speed, activities of daily living, mBMI and autonomic dysfunction met

Adams D, et al. N Engl J Med. 2018;379:11-21

* Improvement defined as patients with <0 point increase from baseline to 18 months

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ONPATTRO™ (patisiran) – Approvals

Approved U.S. Indication — **For the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.**

Data in Label — **Includes data from APOLLO primary and select secondary endpoints.**

"This approval is part of a broader wave of advances that allow us to treat disease by actually targeting the root cause, enabling us to arrest or reverse a condition, rather than only being able to slow its progression or treat its symptoms…New technologies like RNA inhibitors, that alter the genetic drivers of a disease, have the potential to transform medicine, so we can better confront and even cure debilitating illnesses." ***~ Scott Gottlieb, MD, FDA Commissioner, Press Release, 8/10/2018***

Approved EU Indication — **For the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults with stage 1 or stage 2 polyneuropathy.**

Data in SmPC* — **Includes data from APOLLO primary and secondary endpoints, as well as exploratory cardiac endpoints.**

"The safety and efficacy of ONPATTRO was evaluated in a pivotal trial involving 225 patients with hATTR amyloidosis and symptomatic polyneuropathy. The study showed clinically-relevant improvements in the neurological manifestations of the disease and on patients' quality of life, as well as a positive impact on cardiac parameters." ***~ CHMP Opinion Press Release, 7/27/2018***

* SmPC, Summary of Product Characteristics

ONPATTRO U.S. Label Highlights

Dosing & Administration

Dosing:
- 0.3 mg/kg (patients <100 kg)
- 30 mg (patients ≥100 kg)

Premedication (day of infusion):
- IV dexamethasone, 10 mg
- IV H1 and H2 blockers
- Oral acetaminophen

Administration:
- Should be performed by healthcare professional.

Safety

No contraindications

Warnings and Precautions
- Infusion-related reactions: Monitor for signs and symptoms during infusion. Slow or interrupt the infusion if clinically indicated. Discontinue the infusion if a serious or life-threatening infusion-related reaction occurs.
- Reduced serum vitamin A levels and recommended supplementation: Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.

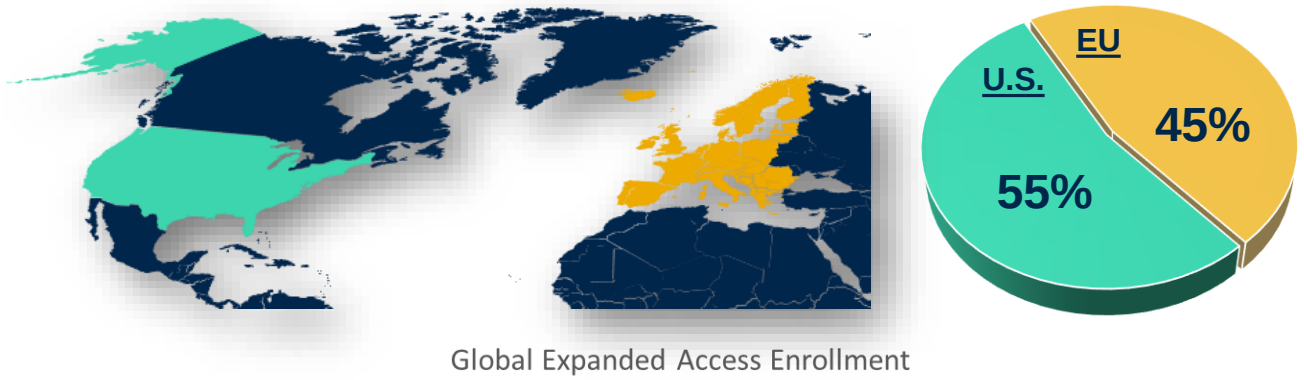
Common adverse reactions are upper respiratory tract infections and infusion-related reactions

No required laboratory monitoring

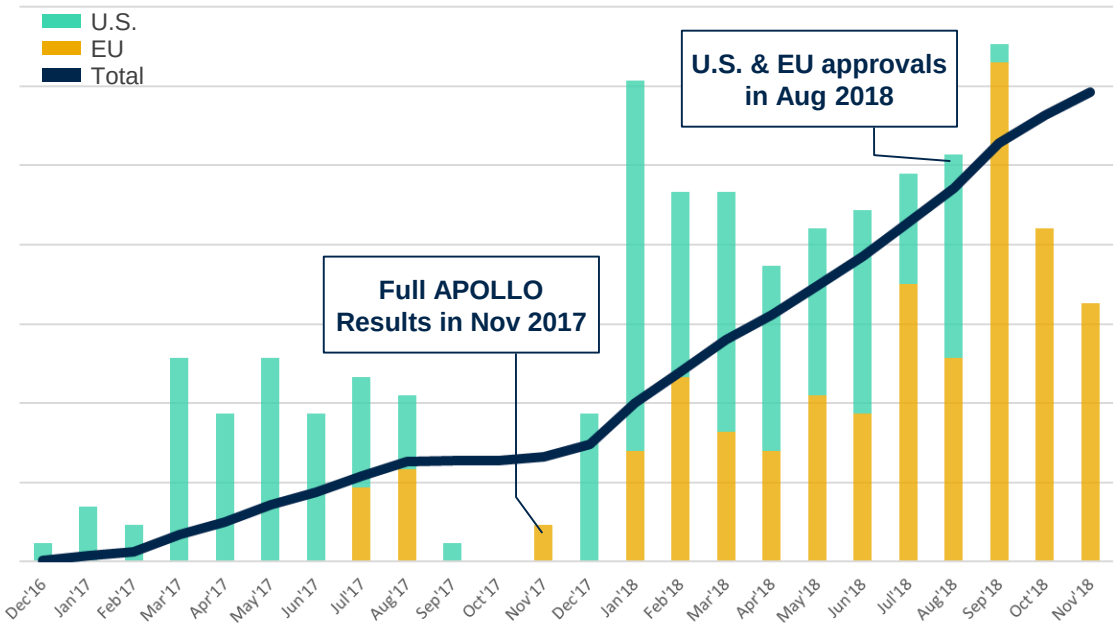
For additional information about ONPATTRO, please see the full Prescribing Information.

Patisiran Expanded Access Program

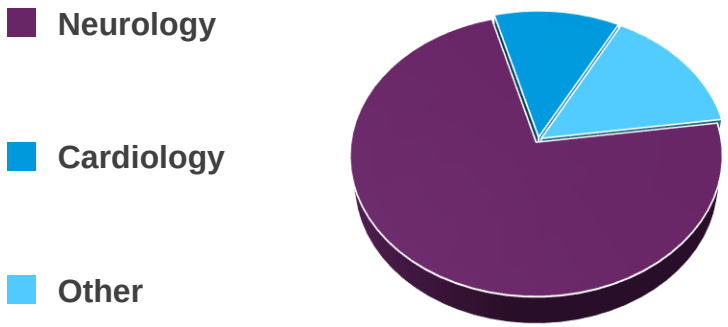
Over 300 Patients Treated in EAP Across U.S. and EU



Global Expanded Access Enrollment



Estimated mix of physician specialties represented across 56 Centers of Excellence (~60% non-APOLLO sites)



Open to eligible patients (APOLLO-like inclusion criteria)

Future Development and Opportunity

R&D Update

- APOLLO results as basis for U.S. and EU labels
- ONPATTRO label expansion opportunity
- Vutrisiran (“*voo-TREE-si-ran*”)*

Commercial Update

- United States
- EU and Canada
- Japan

* Investigational

Pathophysiology of ATTR Cardiac Amyloidosis

Amyloid infiltration leads to ventricular wall thickening and stiffness, resulting in:

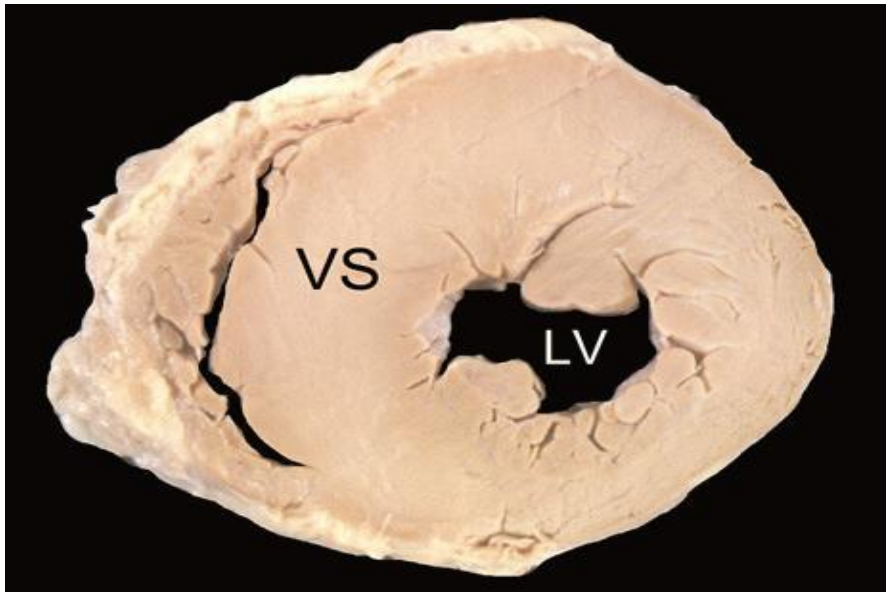
- Diastolic dysfunction
- Systolic dysfunction

NT-proBNP

- Stress biomarker increased in cardiac amyloidosis and congestive heart failure
- Higher NT-proBNP is prognostic factor for worse survival in patients with cardiac amyloidosis*

Patients present with heart failure and cardiac arrhythmias

Cross section of heart with TTR amyloid infiltration



VS: ventricular septum; LV: left ventricle

*Lehrke 2009, Grogan 2016, Damy 2016

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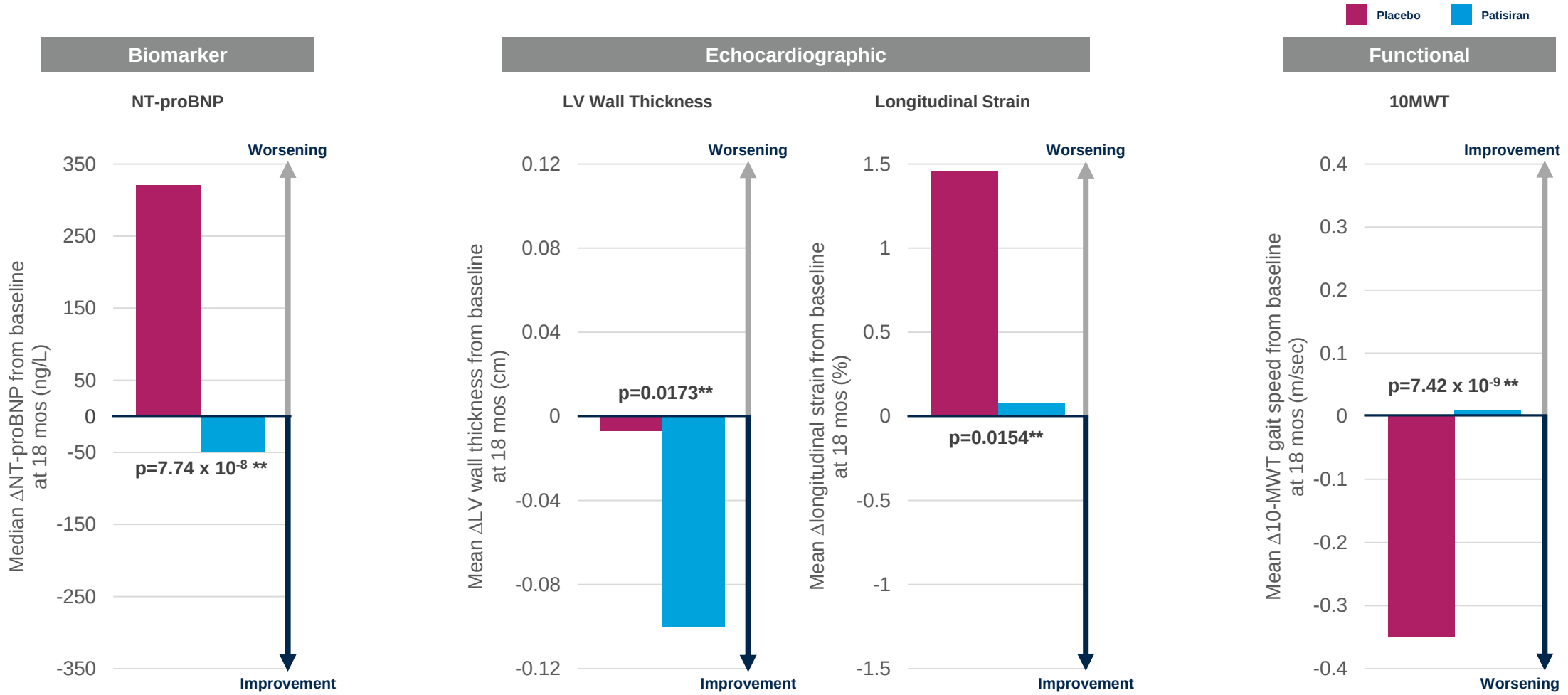
APOLLO Phase 3 Study

Results for Exploratory Endpoints in Cardiac Subpopulation*



Adams D, et al. N Engl J Med. 2018;379:11-21

* Cardiac subpopulation (N=126): patients with pre-existing cardiac amyloid involvement without confounding medical conditions (i.e., patients with baseline LV wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history)

** p-values are nominal

Similar Rates of Cardiac Events Seen in Patisiran and Placebo Groups

APOLLO Phase 3 Study Results

	Placebo* (n=77)	Patisiran* (n=148)
Cardiac AEs, n (%)	28 (36.4)	42 (28.4)
Cardiac SAEs, n (%)	10 (13.0)	20 (13.5)
Cardiac arrhythmia HLGT AEs, n (%)	22 (28.6)	28 (18.9)
Supraventricular arrhythmias HLT	13 (16.9)	15 (10.1)
Cardiac conduction disorders HLT	7 (9.1)	10 (6.8)
Ventricular arrhythmias and cardiac arrest HLT	6 (7.8)	4 (2.7)
Rate and rhythm disorders HLT	0 (0)	5 (3.4)
Deaths, n (%)		
All	6 (7.8)	7 (4.7)
CV	3 (3.9)	7 (4.7)
Cardiac	1 (1.3)	7 (4.7)
Rates of Death/Hospitalization, per 100 py (95% CI)		
Death	6.2 (2.5–12.7)	3.2 (1.4–6.2)
All-cause hospitalization	69.7 (54.3–87.7)	32.9 (25.9–41.1)
Cardiac hospitalization	15.6 (9.0-24.9)	8.2 (5.0-12.6)
Hospitalization and/or death	71.8 (56.1 – 90.1)	34.7 (27.5 – 43.1)
Cardiac hosp and/or death	18.7 (11.4 – 28.8)	10.1 (6.4 – 14.9)

* Summary of cardiac events in the modified intention-to-treat population
† Cardiac arrhythmia AEs were AEs that mapped within the cardiac arrhythmias MedDRA high-level group term that included high-level terms of conduction disorders, rate and rhythm disorders, supraventricular and ventricular arrhythmias, and cardiac arrests
AE, adverse event; CI, confidence interval; HLGT, high-level group term; HLT, high-level term; HR, hazard ratio; RR, rate ratio; SMQ, standard MedDRA query
Solomon S et al. Circulation. 2018

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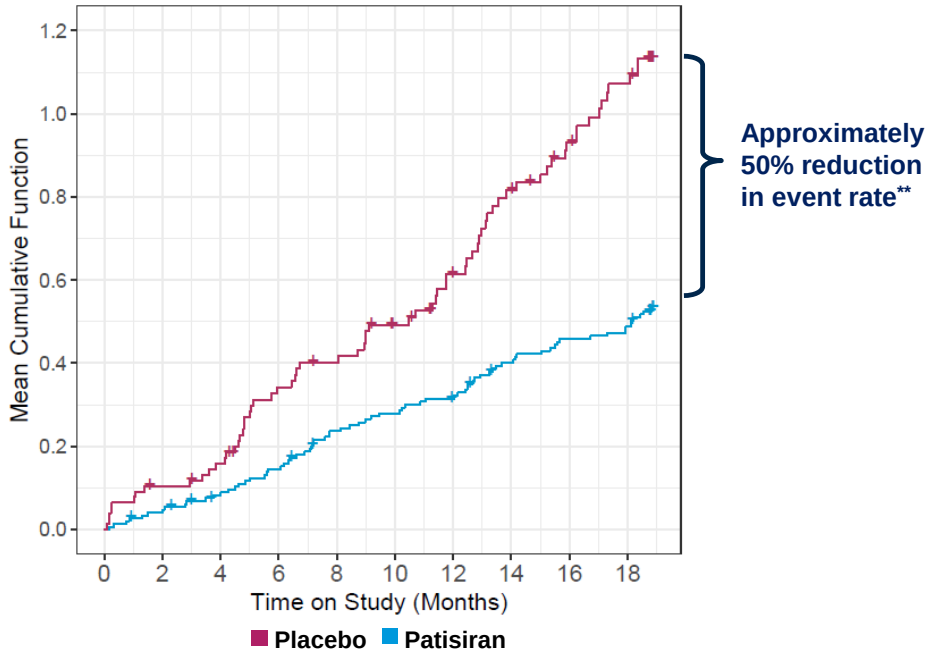
APOLLO Phase 3 Study Results

Recurrent Hospitalization and Death Events by Treatment Arm (Post-Hoc Analysis)*

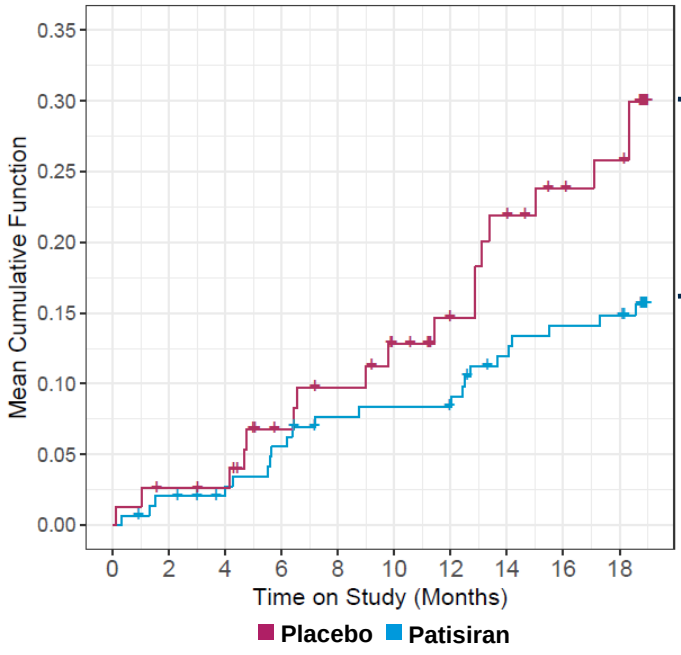
Mean Cumulative Function: average number of events per patient by a certain time

Composite Rate of All-Cause Hospitalization and Mortality



Approximately 50% reduction in event rate**

Composite Rate of Cardiac Hospitalization and All-Cause Mortality



Approximately 45% reduction in event rate†

Analysis of hospitalization/death data was conducted post-hoc based on data collected from AE CRFs; hospitalization/death events caused by SAEs within 28 days of last dose of study drug were included; hospitalization events caused by SAEs within SOC of cardiac disorder were classified as cardiac hospitalization

Exploratory cardiac endpoint data for pre-specified cardiac subpopulation included in SmPC recommended by CHMP but not included in label for U.S. approved by FDA
Solomon S, et al, Circulation 2018
* mITT population
** For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio (HR) 0.48 [0.34, 0.69]
† For cardiac hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.54 [0.25, 1.16]; Anderson-Gill hazard ratio HR) 0.54 [0.28, 1.01]
AE, adverse event; CRF, case report forms; SAEs, serious adverse events; SOC, system organ class

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Key Development Objectives for ONPATTRO

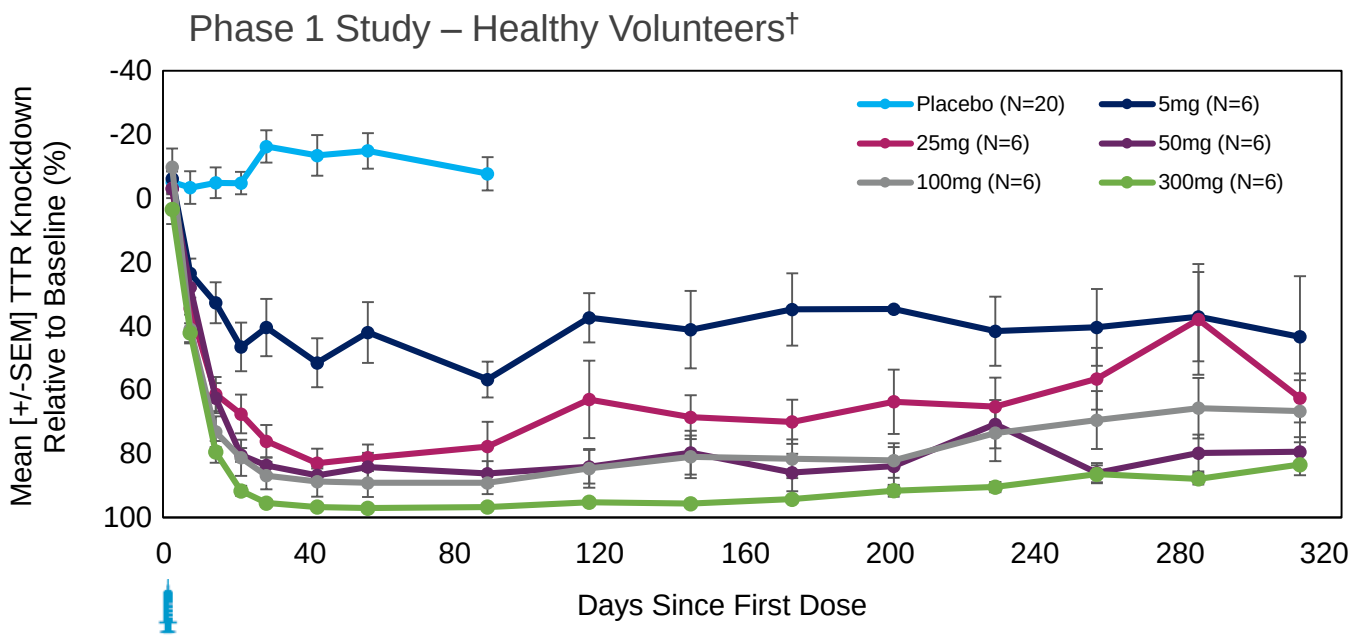
- Demonstrate effects of ONPATTRO on functional capacity or symptoms (e.g., 6MWT or KCCQ) in ATTR amyloidosis patients with cardiomyopathy
- Ongoing discussions with regulatory agencies on study design
- Additional information to be provided when available (expected early 2019)

6MWT, 6-minute walk test; KCCQ, Kansas City Cardiomyopathy Questionnaire`

Vutrisiran Opportunity

Advancing Continued Innovation for Patients with ATTR Amyloidosis

Mean max TTR KD of 83% after single 25 mg dose*



Safety (N=80):

- No SAEs and no discontinuations due to AEs
- All AEs mild or moderate in severity

Vutrisiran

4 **DOSES PER YEAR**

~90% peak TTR KD predicted after repeat dosing

HELIOS-A Phase 3 study **now initiated**

* Taubel J, et al. Phase 1 Study of ALN-TTRsc02, a Subcutaneously Administered Investigational RNAi Therapeutic for the Treatment of Transthyretin-Mediated Amyloidosis. ISA 2018: XVIIth International Symposium of Amyloidosis; Kumamoto, Japan; March 2018 (poster)

† As of data cutoff on 31May2017

Vutrisiran Market Opportunity*

Potential for Significant Expansion in ATTR Amyloidosis

hATTR amyloidosis

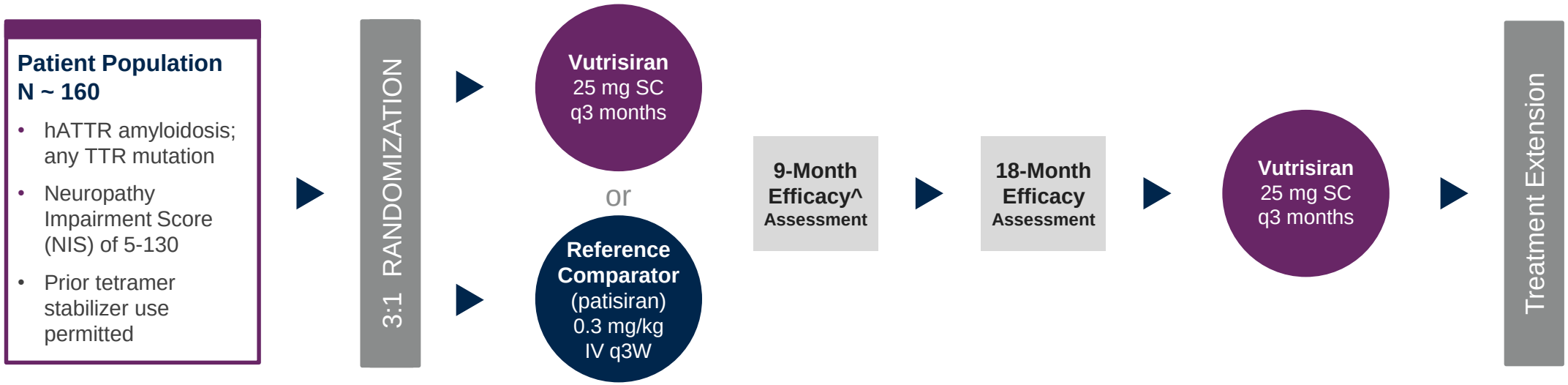
Pre-symptomatic hATTR carriers

Wild-type ATTR amyloidosis patients

* Intended to be illustrative and not intended to represent specific estimates of patient numbers

Vutrisiran Phase 3 HELIOS·A Study

Randomized, Open-Label Study in Hereditary ATTR Amyloidosis Patients



HELIOS·A

Efficacy Assessments (vs APOLLO placebo)

Co-Primary Endpoints
- Change in mNIS+7 from baseline
- Change in Norfolk QOL-DN from baseline

Secondary Endpoints
- 10-meter walk test (10-MWT)
- mBMI
- Activities of daily living (R-ODS)
- TTR reduction (within-study non-inferiority comparison)
- All-cause death and hospitalization (mITT)*
- All-cause death and hospitalization (patients w/ cardiac involvement)*

Exploratory Endpoints Include
- NT-proBNP
- Echo parameters
- Technetium (select sites only, change from baseline)

^ Primary endpoint for the study is at 9 months
* All-cause death and hospitalization endpoints assessed at 18 months only

Alnylam PHARMACEUTICALS

Vutrisiran Development Objectives in ATTR Cardiomyopathy

- Demonstrate effects of vutrisiran on outcomes (e.g., mortality and hospitalizations) in ATTR amyloidosis patients with cardiomyopathy
- Planned discussions with regulatory agencies on study design
- Additional information to be provided when available; HELIOS-B to start in late 2019

ONPATTRO Commercial Progress

R&D Update

- APOLLO results as basis for U.S. and EU labels
- ONPATTRO label expansion opportunity
- Vutrisiran ("*voo-TREE-si-ran*")*

Commercial Update

- United States
- EU and Canada
- Japan

* Investigational

hATTR Amyloidosis Market Opportunity

Estimated Disease Prevalence*

~ 50,000 patients worldwide

NEUROLOGIC PHENOTYPE
> 50% have cardiomyopathy

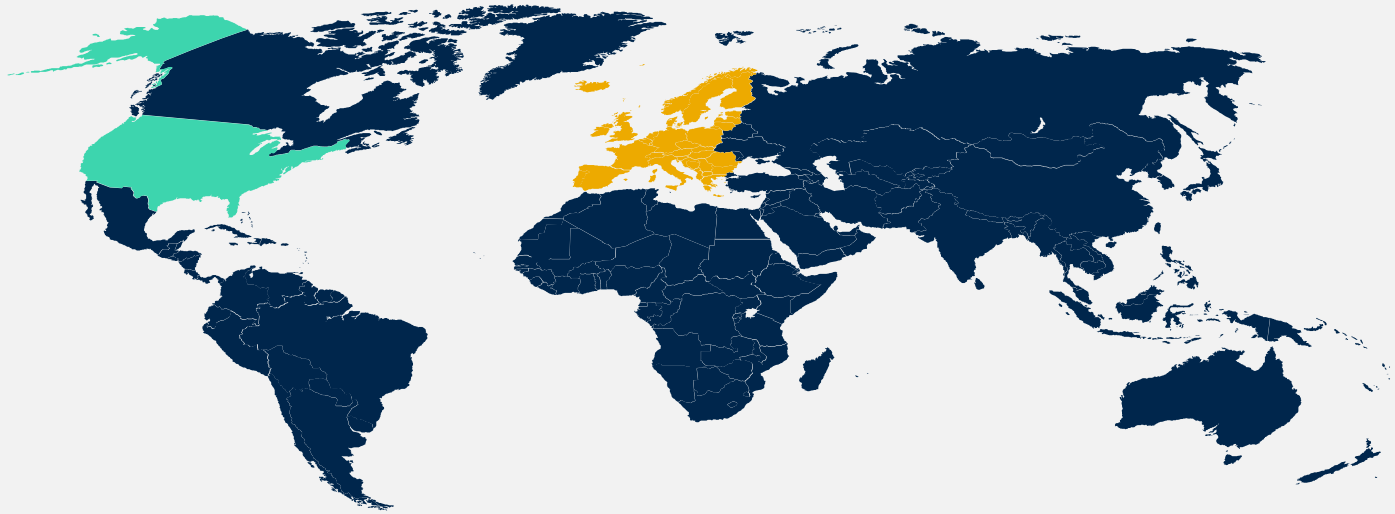
CARDIAC PHENOTYPE†
> 30% have neuropathy

WITHIN ONPATTRO LABEL†

20K to 30K worldwide
~ 10K diagnosed‡

10K to 15K in U.S.
< 3K diagnosed

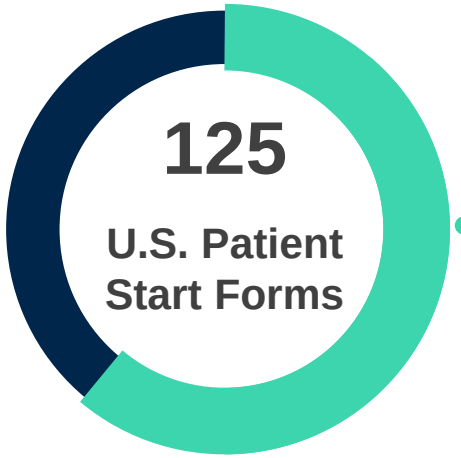
5K to 10K in EU
~ 2K diagnosed



* Based on Alnylam estimates from interviews with key opinion leaders, THAOS registry, recent clinical trials and literature
† ONPATTRO is approved in the U.S. for the polyneuropathy of hATTR amyloidosis in adults, and in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy
‡ Current diagnosis rates difficult to confirm and may be lower in initial launch years

ONPATTRO U.S. Launch Progress

Clinically Proven Approach with Transformational Potential



~60% from patients previously participating in patisiran EAP

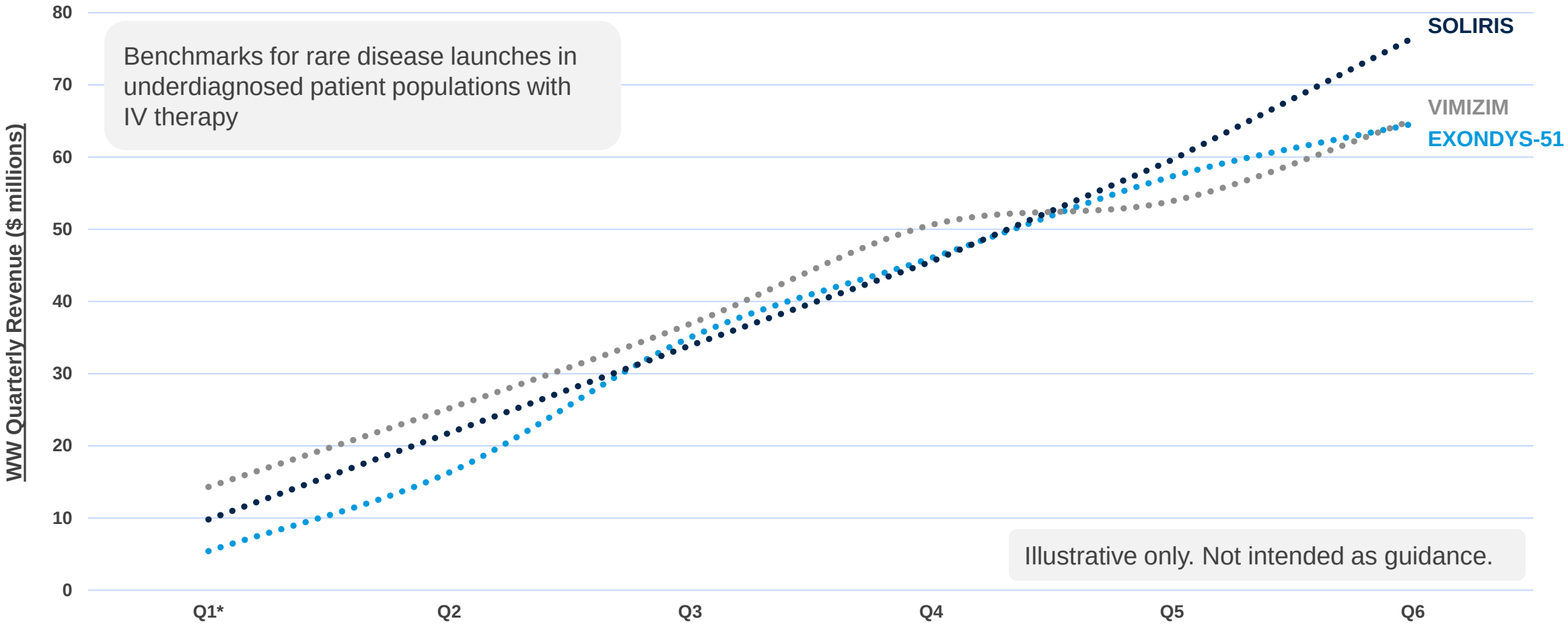
NEUROLOGY CARDIOLOGY HEMATOLOGY

Start Form submissions received from key physician specialties, reflecting both **polyneuropathy & mixed patient phenotypes**

Start Forms are requests submitted to Alnylam Assist patient hub to guide fulfillment of ONPATTRO prescriptions by physicians. Submitted Start Forms do not reflect all demand. Data as of 30Sep2018

Launching a Rare Disease Drug

Analog Launches



* Q1 is first full quarter post-launch

U.S. Medical Affairs & Commercialization Efforts

1 Diagnosis

the BRIDGE™ hATTR amyloidosis

HEREDITARY ATTR AMYLOIDOSIS™

AlnylamAct™

2 Brand Choice

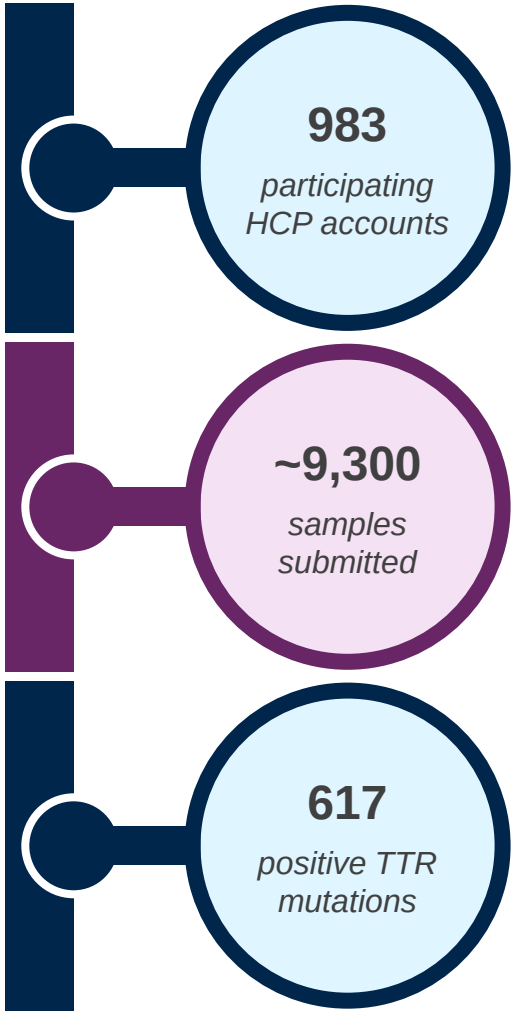
3 Treatment Experience and Access

Alnylam ASSIST™

Aligned Commercial, Market Access, & Medical Affairs teams driving disease education, diagnosis & treatment, optimized patient experience, and access to care

Alnylam PHARMACEUTICALS

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



Reduce barriers to genetic testing and counseling

Tests and services are performed by independent third parties

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

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

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

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

Ongoing Support from Alnylam Assist™

Comprehensive Program Dedicated to Helping Guide Patients Through Treatment with ONPATTRO

Dedicated Case Manager
Alnylam Assist will connect patients with dedicated Alnylam Case Manager who can provide personalized support throughout treatment process.

Benefit Verification
Coverage for ONPATTRO will vary by plan and by patient. Alnylam Assist can help determine patient-specific coverage requirements.

Financial Assistance for Patients
Eligible patients may qualify for Alnylam Assist Quick Start Program, Patient Assistance Program (PAP), or Commercial Copay Program.

Treatment Coverage
Alnylam Assist can explain requirements and processes for prior authorizations, claims, and appeals.

Coding and Billing
A Field Reimbursement Director can provide education about billing, coding, and reimbursement process for ONPATTRO.

Disease and Product Education
Patient Education Liaisons are available to help patients gain better understanding of disease.

Ordering Assistance
Alnylam Assist will help with ordering and facilitation of delivery via specialty distributor or specialty pharmacy.

Alnylam ASSIST™

8AM–7PM ET, Monday–Friday
1-833-256-2748 | 1-833-256-2747
To learn more about Alnylam Assist, visit www.AlnylamAssist.com.

Alnylam PHARMACEUTICALS

From Start Form to Infusion

Anticipate Significant Timeline Reduction Over Next Few Quarters

Current estimated average time to infusion	Alnylam goal for time to infusion
2 – 4 months	**<8 weeks**

ONPATTRO Value-Based Agreements (VBAs)

Demonstrating Commitment to Patient Access

Proactively Engage & Educate Payers

Enable Patient Access to ONPATTRO

Ensure Value Delivered

Agreed upon term sheets with payers covering >80% of commercially insured lives

* Subject to best price protection

Europe and Canada Highlights

Continued Progress in EUCAN and Regulatory Filings in Additional Countries

Germany

- **Price listed 01 October 2018**
- >30 patients on EAP; transitioning to ONPATTRO
- ONPATTRO treatment also initiated for patients newly diagnosed and transitioned from other treatments
- Home infusions ongoing

Austria

- **Price listed 01 November 2018**
- EAP patients transitioning to ONPATTRO
- Named patient sales about to be initiated in newly diagnosed patients and patients progressing under TTR stabilizer treatment

Canada

- **NDS filed 13 November 2018**
- Approval expected in mid-2019
- Received EAP requests

Switzerland

- **MAA filed 03 December 2018**
- Approval expected in late 2019
- Named patient sales ongoing

Strong progress in other markets with patient access expected in 2019

EAP – Expanded Access Program; NDS – New Drug Submission; MAA – Market Authorisation Application

Japan

Alnylam K.K. Established to Commercialize Directly

hATTR Amyloidosis

- **Estimated ~400 patients diagnosed**
- Predominantly polyneuropathy and mixed phenotypes
- Two endemic regions (Kumamoto and Nagano)

Organization

- **Country and regional leadership in place**
- Medical Affairs lead in place; MSLs expected Q1’19
- Commercial field team expected Q2’19

Regulatory

- **JNDA filed 27 September 2018**
- Potential approval in mid-2019

Communicating ONPATTRO Launch Progress

Anticipated Timeline of Disclosures

√ = First Disclosure √ = Ongoing Disclosure

	Q3 2018 Results	*J.P. Morgan 2019*	*FY 2018 Results & Quarterly through 2019*
Global Product Revenue	√	√*	√
Submitted U.S. Start Forms	√	√	√
Percent Previously on EAP	√	√	√
Patients on Commercial Drug		√	√
Total Patients on Drug		√	√
U.S. Payer Mix		√	√
U.S. Prescriber Mix		√	√

* Unaudited revenue

Alnylam ATTR Amyloidosis Franchise

Expanding Value to Patients Globally for Many Years to Come

2019 – 2021

onpattro* (patisiran) lipid complex injection — *PN & Mixed*

2021 – 2023

Vutrisiran† — *PN & Mixed*

onpattro‡ (patisiran) lipid complex injection — *PN, Mixed, & CM*

2023 & Beyond

Novel siRNA Conjugates — *Ocular & CNS hATTR Amyloidosis*

Vutrisiran — *PN, Mixed, & CM, Wild-Type, & Carriers*

onpattro (patisiran) lipid complex injection — *PN, Mixed, & CM*

* ONPATTRO is approved in the U.S. for the treatment of the polyneuropathy of hATTR amyloidosis in adults, and in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy

‡ ONPATTRO has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population

† Vutrisiran has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding the safety or effectiveness of this investigational therapeutic

Intended to be illustrative and not intended to represent specific estimates of patient numbers

Alnylam PHARMACEUTICALS

Acute Hepatic Porphyria & Givosiran

John D. Phillips, Ph.D., University of Utah

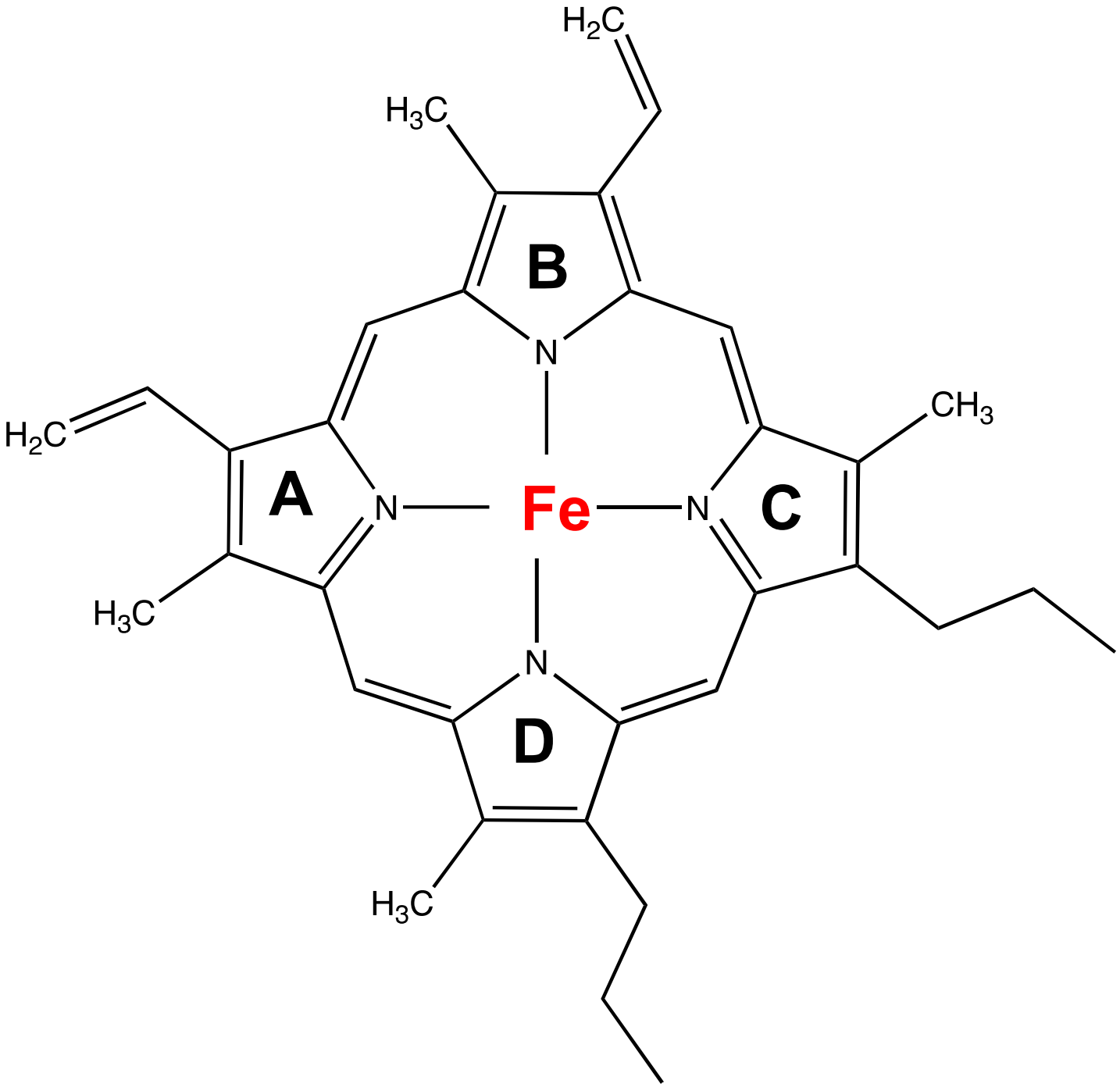
Akin Akinc, Ph.D., VP & General Manager, Givosiran

Alnylam® PHARMACEUTICALS

Acute Hepatic Porphyrias
New therapies for old diseases

John D. Phillips, Ph.D.

December 6, 2018


H2C
H3C
B
N
CH3
H2C
A
N
Fe
N
C
H3C
N
D
H3C

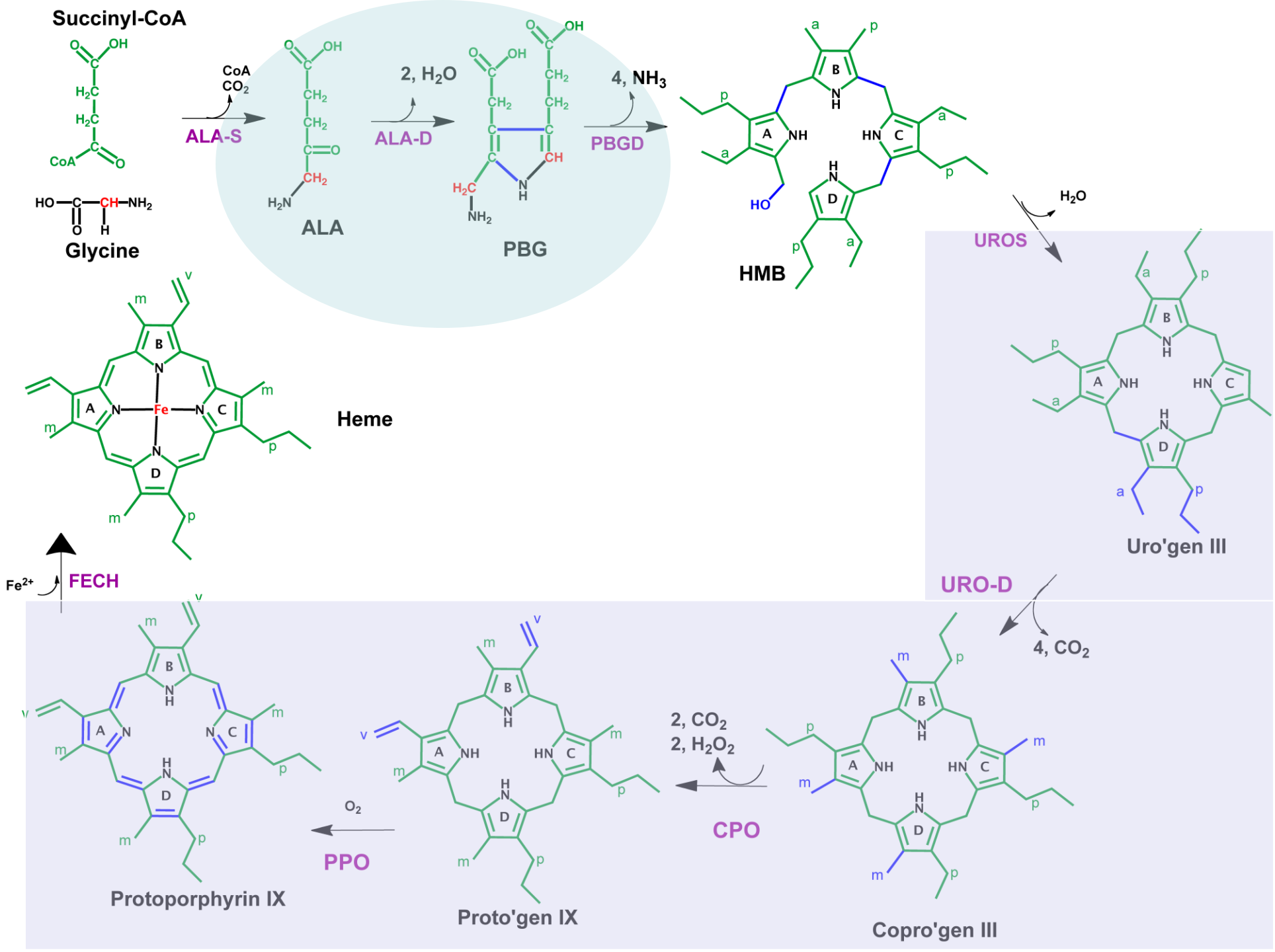
Disclosures

- Consulting
  - Agios
  - Alnylam
  - Mitsubishi Tanabe
  - Recordati Rare Disease
  - Clinuvel

The Porphyrias

A group of disorders due to subnormal activity of enzymes in the heme biosynthetic pathway

Substrates of affected enzymes accumulate and determine the phenotype


Succinyl-CoA
CoA
CO2
ALA-S
ALA
2, H2O
ALA-D
PBG
4, NH3
PBGD
HMB
H2O
UROS
Uro'gen III
Glycine
Heme
Fe2+
FECH
URO-D
4, CO2
Copro'gen III
2, CO2
2, H2O2
CPO
O2
PPO
Proto'gen IX
Protoporphyrin IX

Rate Limiting Steps

Rate Limiting Steps

Porphyria Frequency

- Most prevalent
  - Porphyria cutanea tarda 30:100,000
  - **Acute intermittent porphyria 4:100,000**
  - Erythropoietic protoporphyria 1:100,000

- Rare
  - **Hereditary coproporphyria**
  - **Variegate porphyria**

- Very rare
  - Congenital erythropoietic porphyria
  - **ALA-D porphyria**

Clinical Spectrum of Porphyrias

Cutaneous photosensitivity

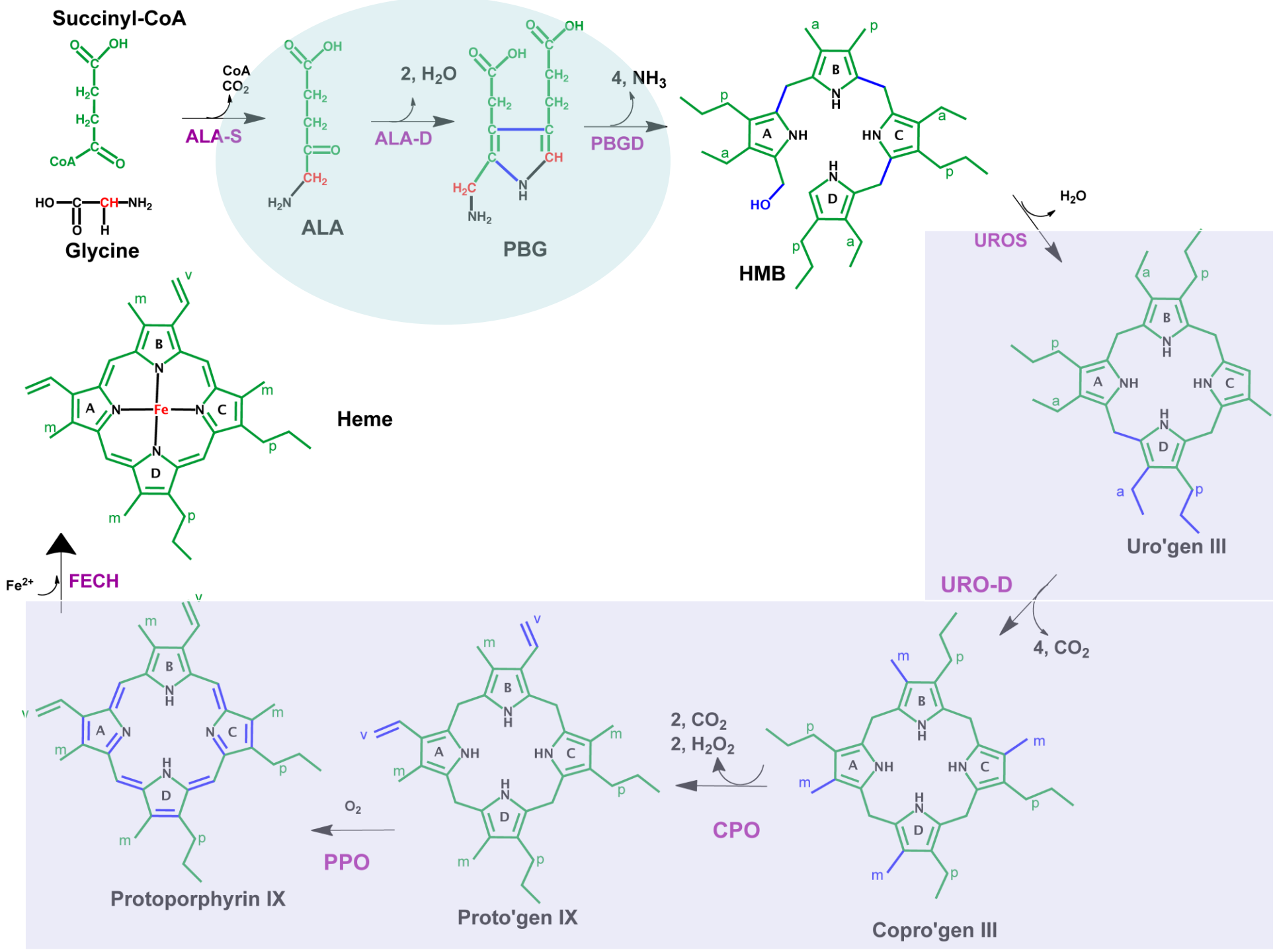
- Congenital erythropoietic porphyria
- Porphyria cutanea tarda
- Erythropoietic protoporphyria

Neurovisceral

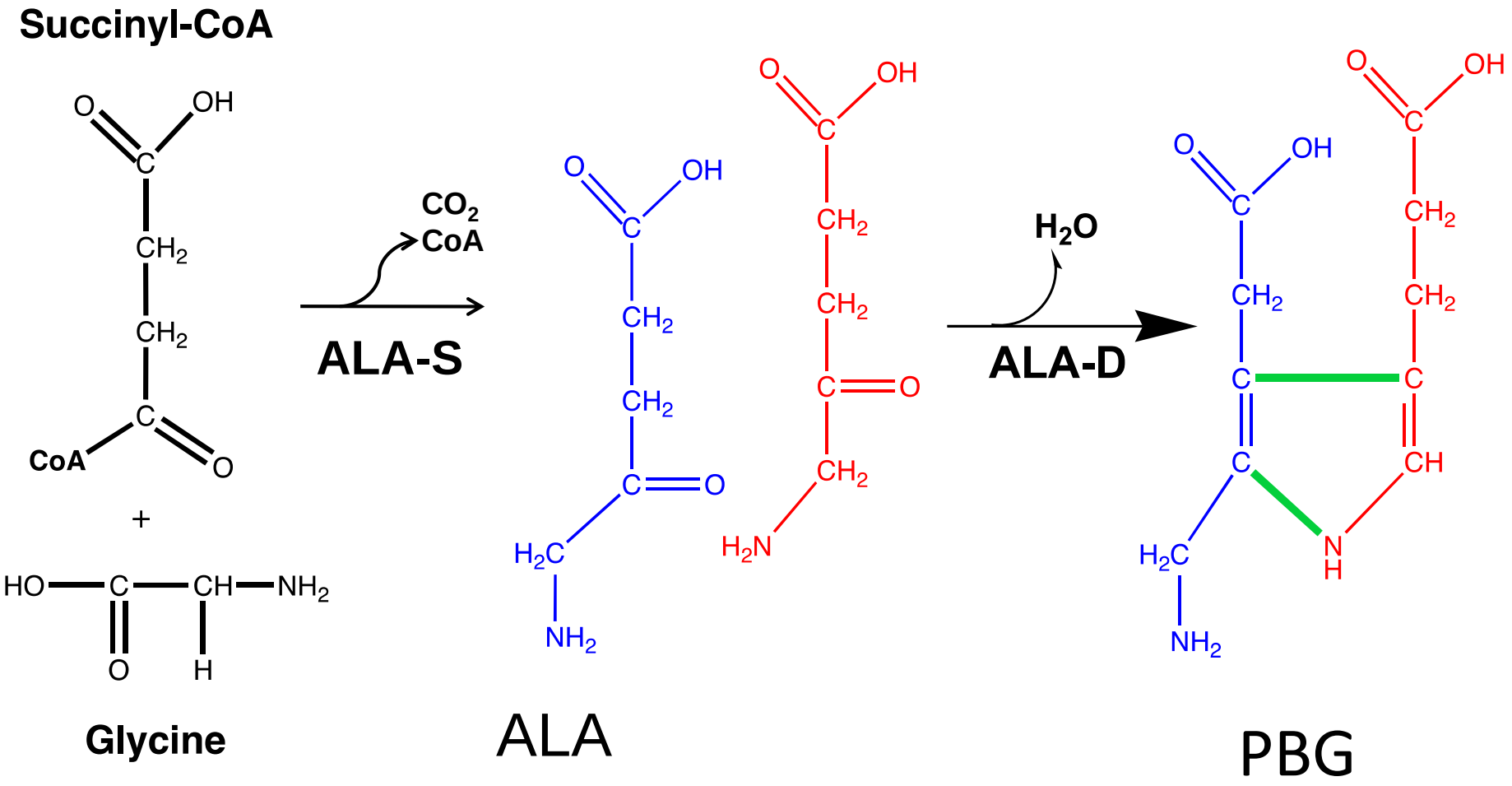
- ALAD deficiency
- Acute intermittent porphyria

Neurovisceral and cutaneous photosensitivity

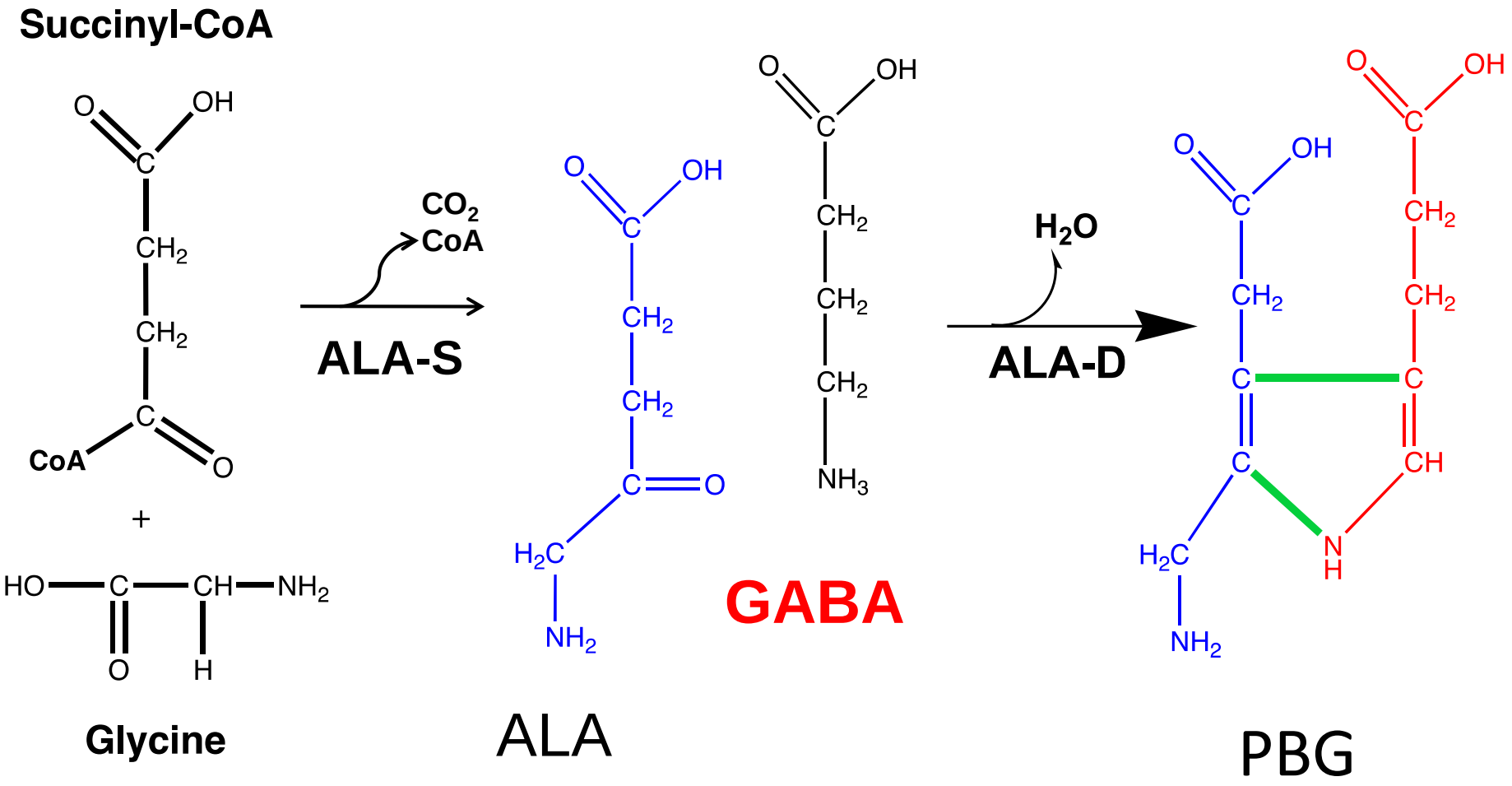
- Hereditary coproporphyria
- Variegate porphyria


Succinyl-CoA
Glycine
CoA
CO_2
ALA-S
ALA
2, H_2O
ALA-D
PBG
4, NH_3
PBGD
HMB
H_2O
UROS
Uro'gen III
URO-D
4, CO_2
Copro'gen III
2, CO_2
2, H_2O_2
CPO
O_2
PPO
Proto'gen IX
Protoporphyrin IX
Fe^{2+}
FECH
Heme

Assembly of the Pyrrole



Assembly of the Pyrrole

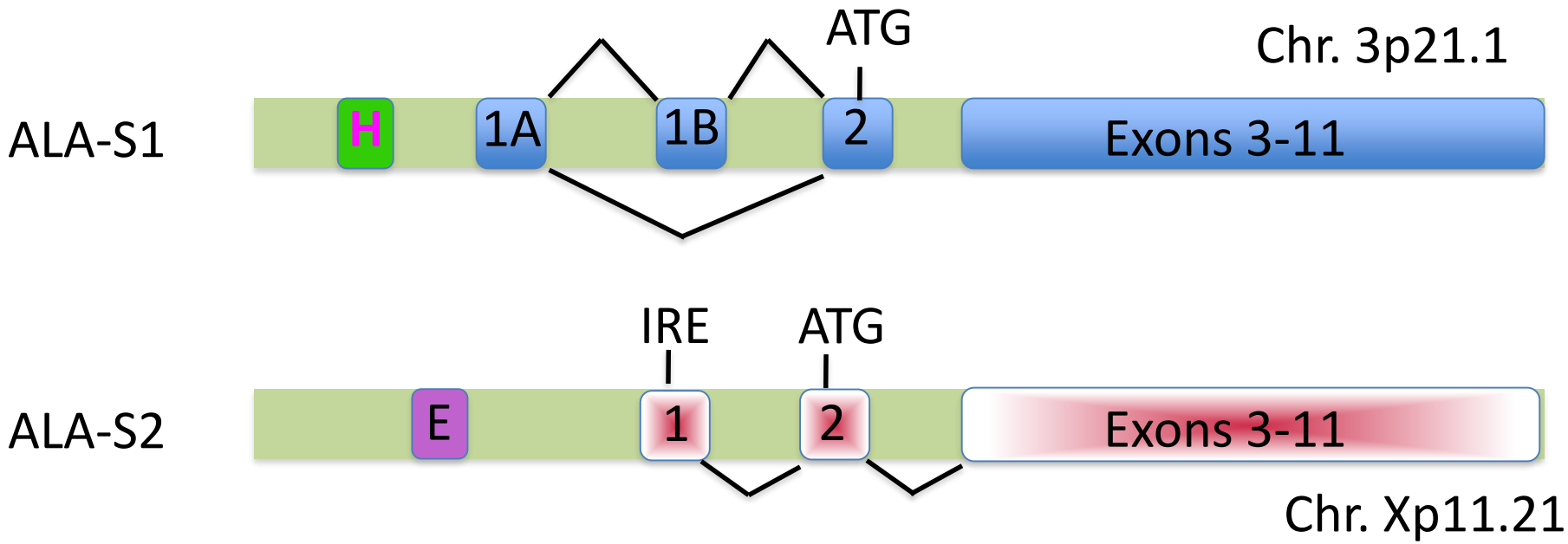


Regulation of Heme Biosynthesis

- Liver - responds to changing metabolic requirements ~15% of daily synthesis

- Red cells - high steady state level, tied to availability of iron ~80% of daily synthesis

Two ALA Synthases



Acute Intermittent Porphyria (AIP)

Neurologic

- Pain
- Paresis
- Respiratory paralysis
- Mental symptoms
- Convulsions

Onset after puberty

- Female:Male = 5:1

AIP

Pathogenesis of the acute attack

1. Heme depletion and induction of ALA-S1

2. Accumulation and secretion of PBG & ALA

Attack Symptoms

Autonomic neuropathy

- Abdominal pain vomiting, nausea, constipation
- Tachycardia, arrhythmia, labile hypertension
- Diaphoresis

Acute peripheral neuropathy

- Muscle weakness
- Neuropathic sensory loss
- Respiratory paresis due to diaphragm paresis

CNS manifestations

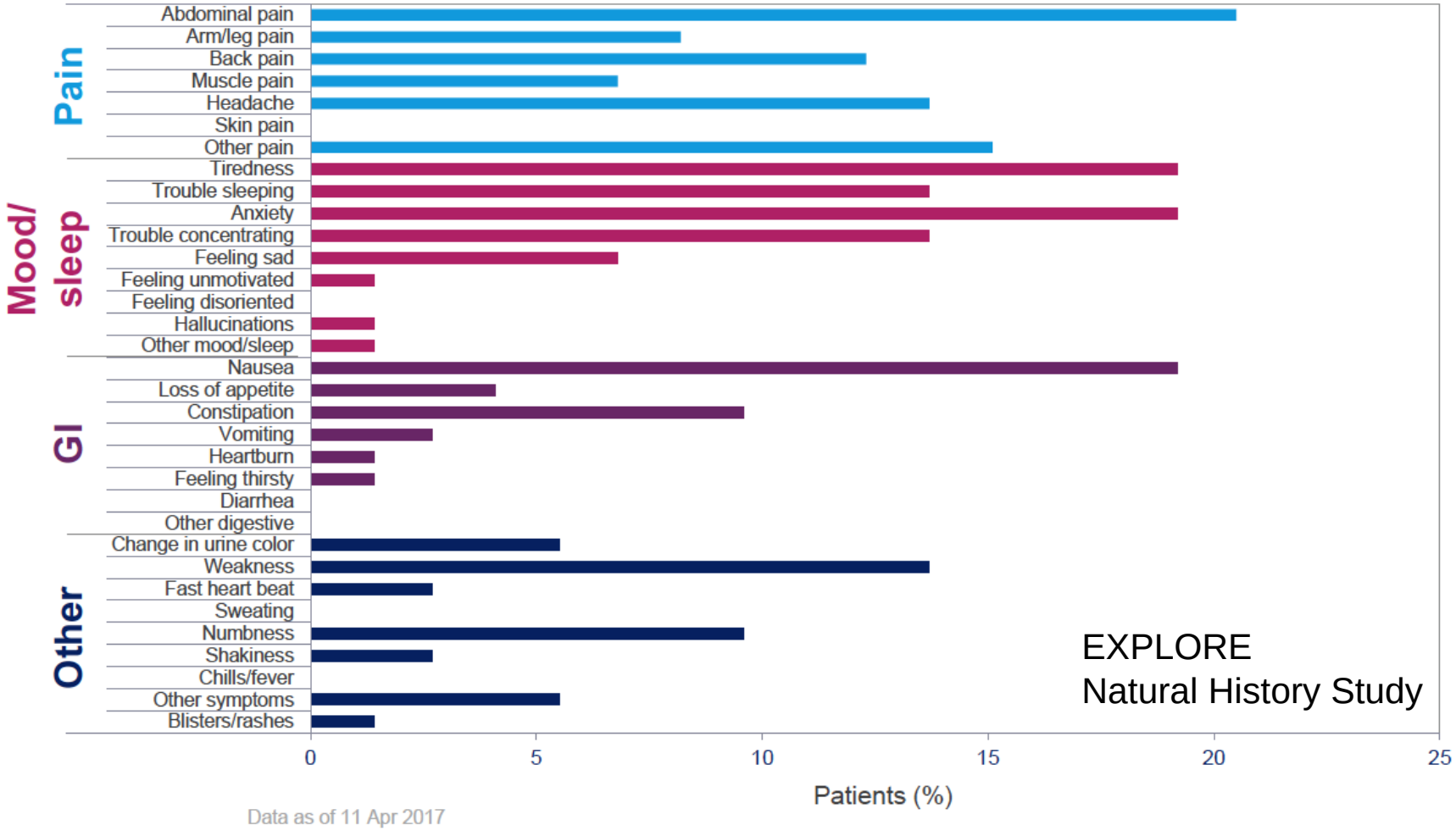
- Anxiety, confusion, insomnia, depression, agitation, hallucinations
- Acute encephalopathy, headache, somnolence, altered mental status

Metabolic changes

- Hyponatremia
- Mild LFT elevation

Chronic Symptoms

Baseline Patient-Reported Chronic Symptoms



Data as of 11 Apr 2017

65% Chronic symptoms

46% Daily symptoms

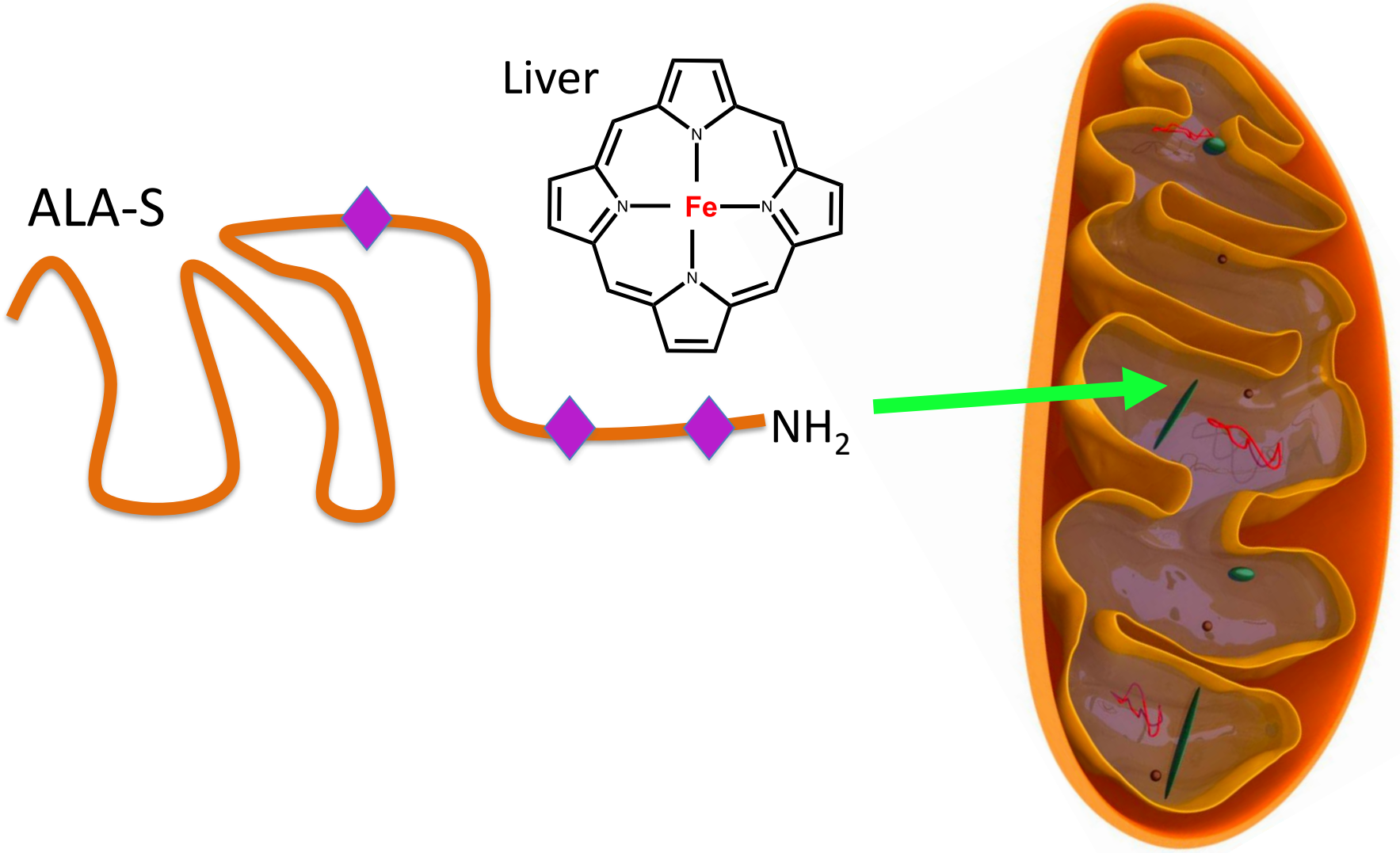
Disease Management

- Identify precipitating factors – modify lifestyle
  - Drugs: barbiturates, sulfonamides, strong P450 inducers
  - Alcohol
  - Luteal phase of the menstrual cycle
  - Stress, infections
  - Fasting
  - Surgery

Disease Management

- Identify precipitating factors – modify lifestyle
- Treatment of symptoms
- Carbohydrate loading – may work for mild attacks
  - Caloric intake
  - Hyponatremia – electrolyte infusion
  - Panhematin®
    - 3-4 mg/kg body weight, 4 consecutive days
    - Dissolved in 100 mL human albumin (4-20%)

Regulation of ALA-S1



Disease Management

- Identify precipitating factors – modify lifestyle
- Treatment of symptoms
- Carbohydrate loading – may work for mild attacks
  - Caloric intake
  - Hyponatremia – electrolyte infusion
  - Panhematin®
    - 3-4 mg/kg body weight, 4 consecutive days
    - Dissolved in 100 mL human albumin (4-20%)
- RNAi to ALAS1
- Liver transplant

Longer-term Disease Manifestations

- Chronic kidney disease
- Liver disease
- Hepatocellular carcinoma

Unmet Needs

- **Natural history of acute porphyrias**
  - What other genetic and environmental factors drive disease expression?
  - Who will become recurrent?
- **Biomarkers to assist clinical management**
  - To better monitor and assess severity of acute attack
  - Who are at risk to develop late complications?
- **New treatments**
  - Acute attack treatment
  - Prophylaxis to prevent attacks
  - But also to prevent late complications

https://www.youtube.com/watch?v=urHxVYVAals


James Kushner
Hector Bergonia
Charles Parker
Laurie Jackson
Colin Farrell
The Porphyrias Consortium
NIDDK-RO1-090257
NIDDK-U54-083909

Givosiran

Akin Akinc, Ph.D.

VP & General Manager, Givosiran

Alnylam® PHARMACEUTICALS

Nichol
Living with Porphyria

Acute Hepatic Porphyria

Givosiran

Description

Family of ultra-rare orphan diseases causing incapacitating and potentially fatal attacks, leading to frequent hospitalizations and chronic pain

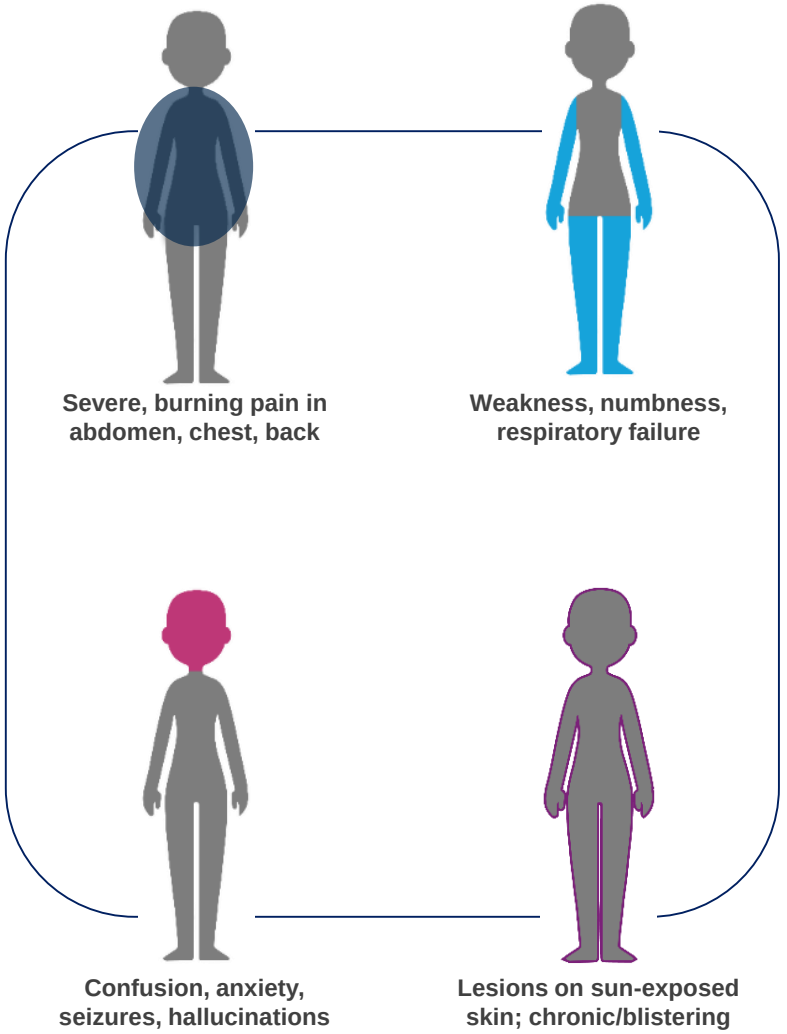
Predominantly

female,

commonly misdiagnosed

Patient Population*

~5,000	~1,000
Patients with **sporadic attacks** in U.S./EU	Patients with **recurrent attacks** in U.S./EU

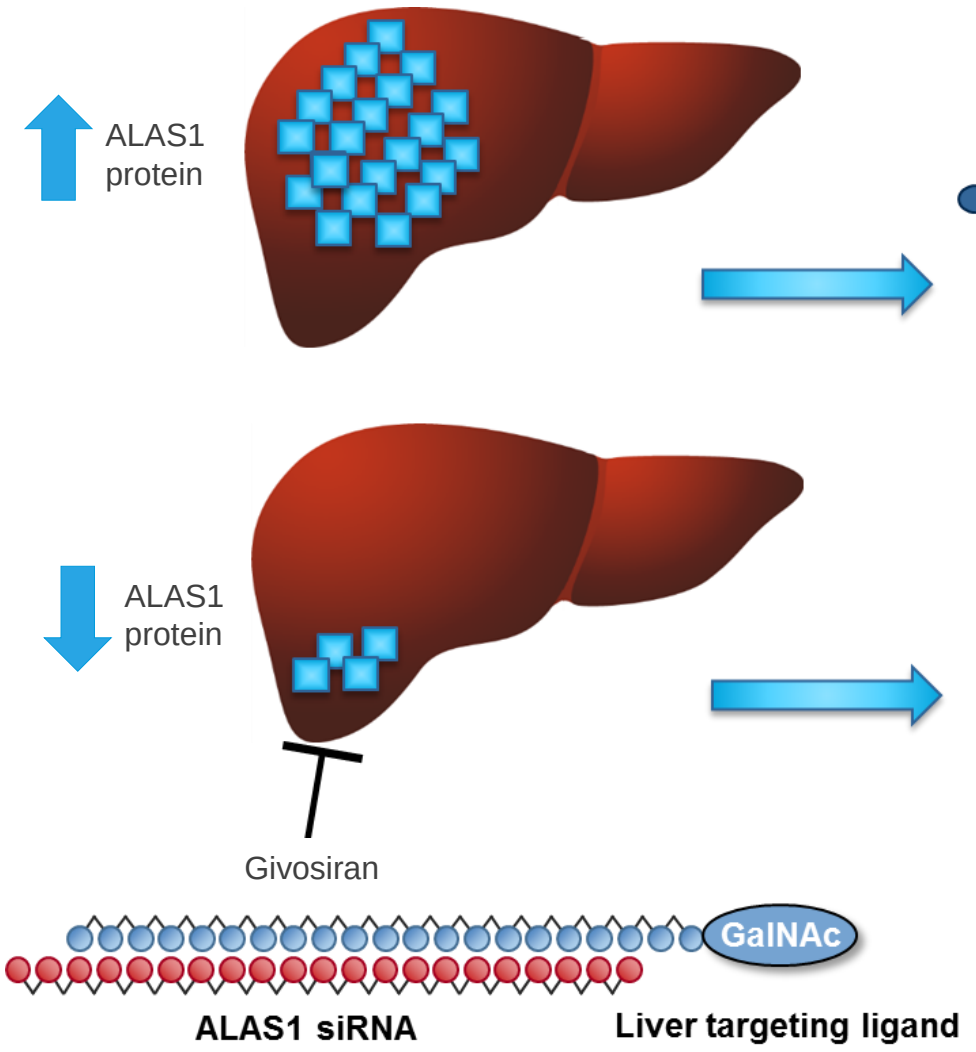


* ORPHANET; The Porphyria Consortium

Alnylam PHARMACEUTICALS

Givosiran Therapeutic Hypothesis

Reduction of Liver ALAS1 Protein to Lower ALA and PBG



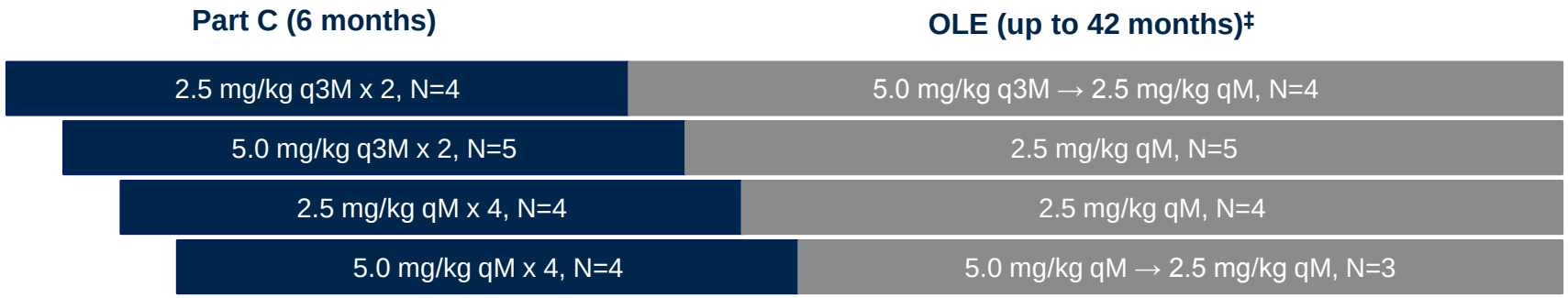
ALA induces porphyria symptoms

Givosiran results in reduction of ALAS1 and lowers ALA/PBG production to prevent attacks and disease symptoms

ALA; δ-Aminolevulinic acid. PBG; Porphobilinogen. ALAS1; ALA synthase 1

Phase 1 Part C and Phase 1/2 OLE Overview

Studies in Recurrent Attack Patients



Phase 1 Part C

- Randomized 3:1 (givosiran:placebo), double-blind design
- Genetic confirmation of AIP
- Observational run-in (3 month) without scheduled hemin
- ≥2 attacks in past 6 months OR on prior hemin prophylaxis. One attack in run-in required for randomization
- Patients completing Part C eligible to enroll in OLE

Phase 1/2 OLE*

- All eligible patients from Phase 1 Part C enrolled into OLE
- Mean time in OLE of 13.6 months (median 14.3 months)
- Max time in OLE of 19 months, with max of 25 months of total treatment in Phase 1 and OLE

‡All patients in OLE transitioned to 2.5 mg/kg qM; Safety Review Committee authorization before all dose escalations
*Data as of 7Jun2018

Safety and Tolerability

Interim Phase 1/2 OLE Study Results

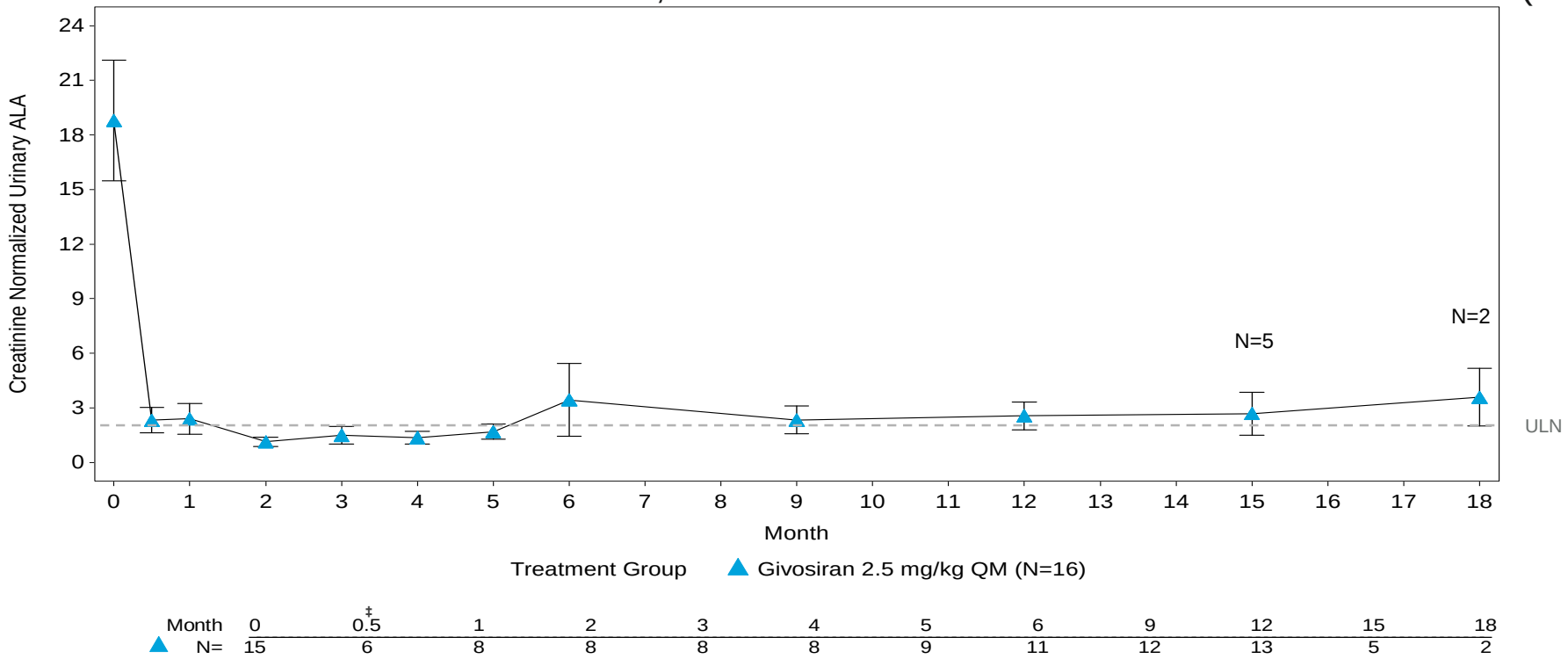
- 100% (16/16) patients reported at least 1 AE
- 4 patients with 5 SAEs
  - 1 patient with upper extremity DVT, unlikely related to study drug due to prior indwelling central venous catheter and venous damage from chronic hemin usage
  - 1 patient with anaphylactic reaction, assessed as definitely related to study drug:
    - Occurred after third dose of givosiran (first dose in OLE at 2.5 mg/kg); patient previously received two doses (5 mg/kg q3M) in Phase 1 study
    - Past history of asthma and atopy
    - Event resolved with medical management, and patient permanently discontinued from study
  - 1 patient had two events: two episodes of pyrexia related to suspected PaC infection and chlamydia bronchitis; all events assessed as unlikely related
  - 1 patient with change in mental status due to possible glucocorticoid toxicity for an acute bacterial sinusitis, assessed as unlikely related
- AEs in >3 patients: abdominal pain, fatigue, injection site erythema, nausea, myalgia, diarrhea, headache, and nasopharyngitis
- 6 patients had injection site reactions, most commonly erythema and all mild to moderate
- No clinically significant increases in LFTs or lipase with ongoing dosing

Data as of 7Jun2018; Anderson *et al*. AASLD Nov 2018

Consistent and Durable Lowering of ALA Toward Normal Levels with Long-term Givosiran Dosing

Interim Phase 1/2 OLE Study Results

- Monthly dosing at 2.5 mg/kg led to robust and sustained lowering of ALA toward normal levels, with a reduction from baseline of 87% at Month 12
- Similar reductions were seen with PBG, with a reduction from baseline of 83% at Month 12 (data not shown)



Data as of 7Jun2018; Anderson *et al*. AASLD Nov 2018

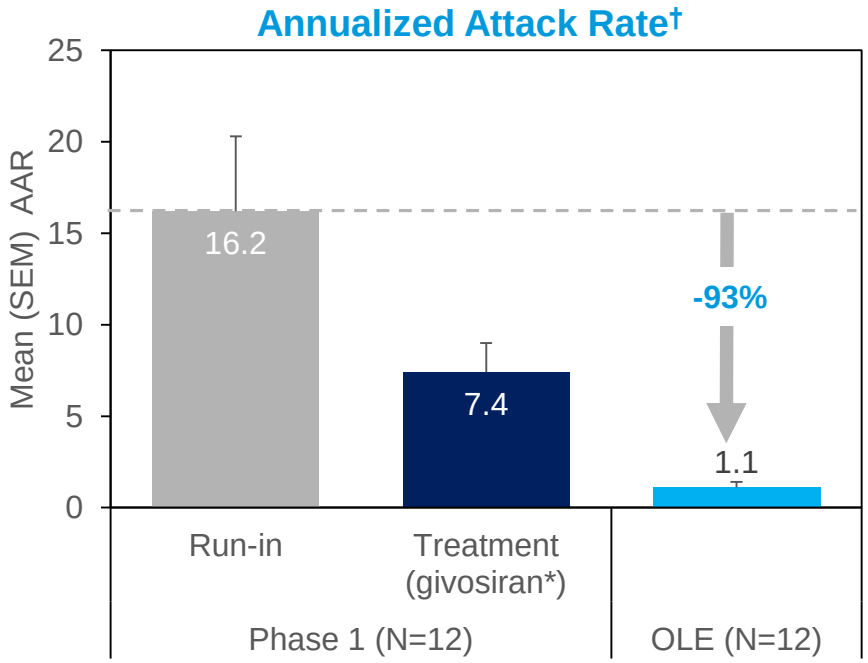
[1]Upper Limit of Normal (ULN): ALA=1.5 mmol/mol Cr

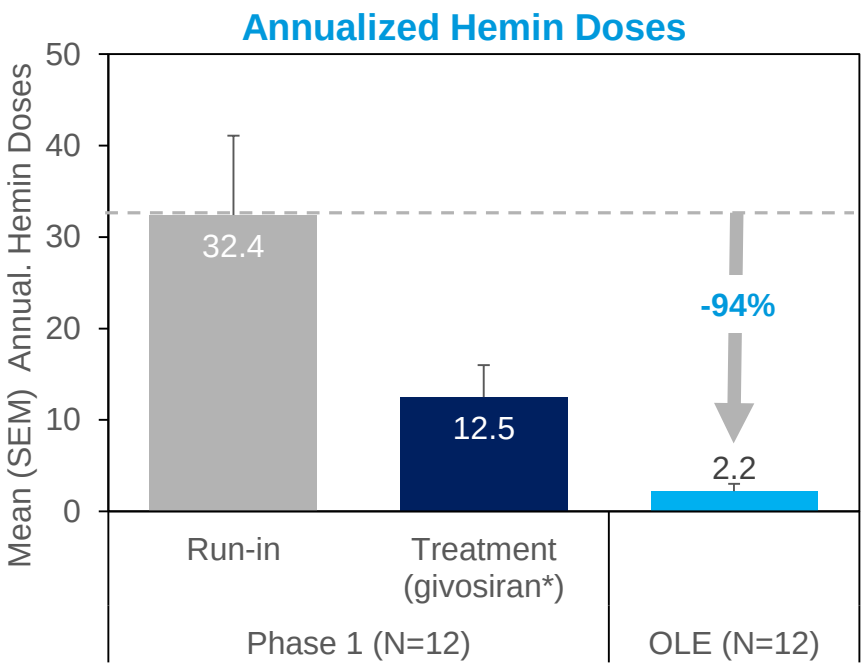
‡The different Ns at each month reflect differences in (1) when patients transitioned to 2.5 mg/kg dose on study, and (2) the duration of patients on study. The N=15 at 0 month reflects a missing data point at pre-study baseline.

Clinical Activity Maintained or Enhanced in Givosiran Treated Patients with Extended Dosing in OLE Study

Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

- Mean reductions in AAR of 93% and annualized hemin use of 94% observed in OLE relative to Phase 1 Run-in
- 5/12 (42%) patients with AAR = 0, for a mean of 7.4 months





Data as of 7Jun2018; Anderson et al. AASLD Nov 2018

OLE: Open-label extension. AAR: Annualized attack rate

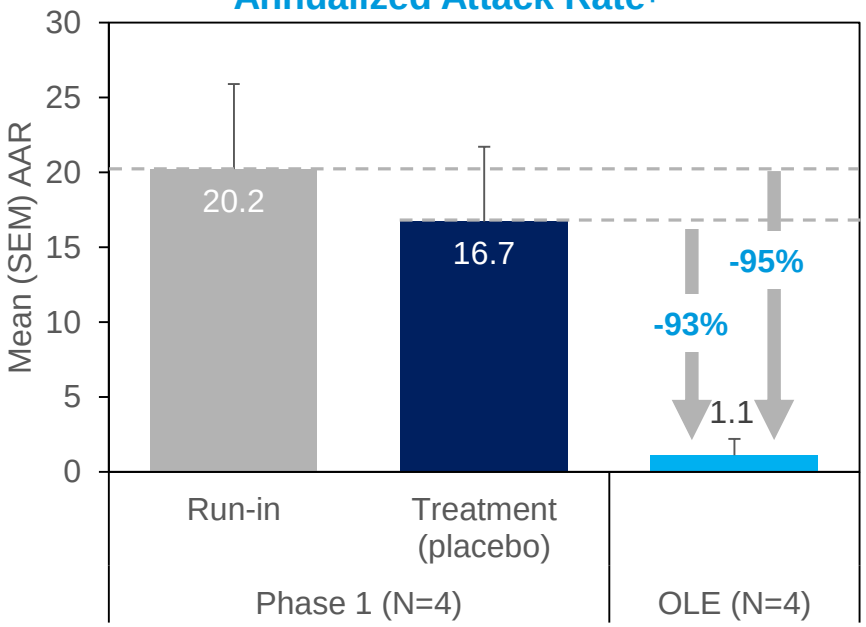
†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home. *Aggregated across all dose groups. Mean time in Phase 1 Run-in and Treatment of 103 days and 165 days, respectively; mean time in OLE of 415 days.

Clinical Activity Demonstrated in Placebo Patients Crossing Over to Givosiran Treatment in OLE

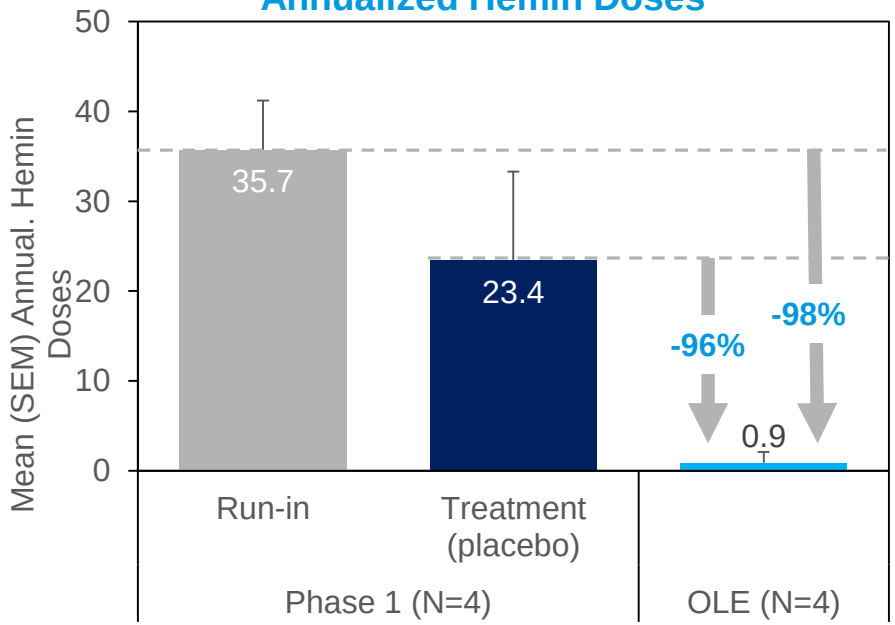
Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

- Upon crossing over to givosiran in OLE, prior Phase 1 placebo patients had a 95% mean reduction in AAR and 98% mean reduction in annualized hemin use relative to both Phase 1 Run-in and Treatment periods
- 2/4 (50%) patients with zero attacks, for a mean of 14.6 months

Annualized Attack Rate†



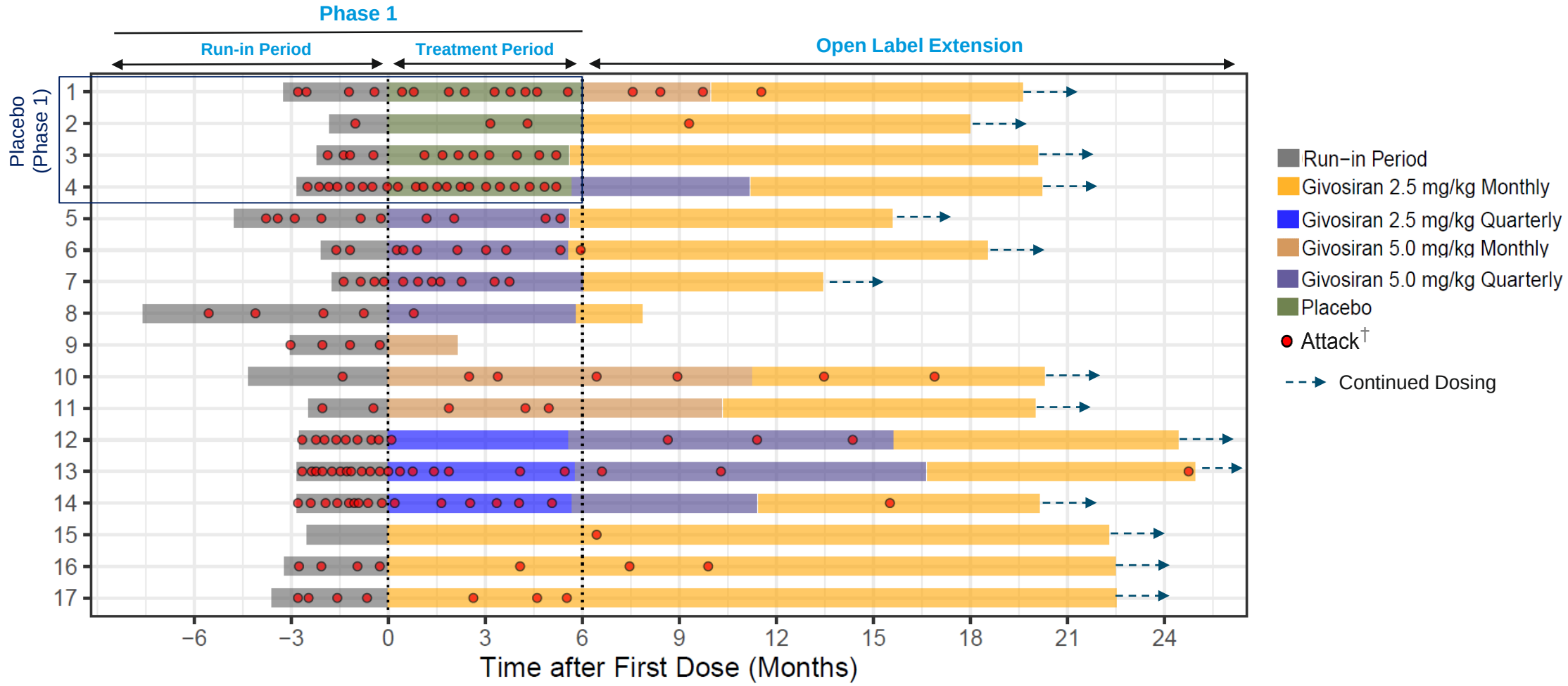
Annualized Hemin Doses



Data as of 7Jun2018; Anderson *et al*. AASLD Nov 2018. OLE: Open-label extension. AAR: Annualized attack rate
†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home. Mean time in Phase 1 Run-in and Treatment of 77 days and 175 days, respectively; mean time in OLE of 416 days

Clinical Activity in Recurrent Attack Patients

Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

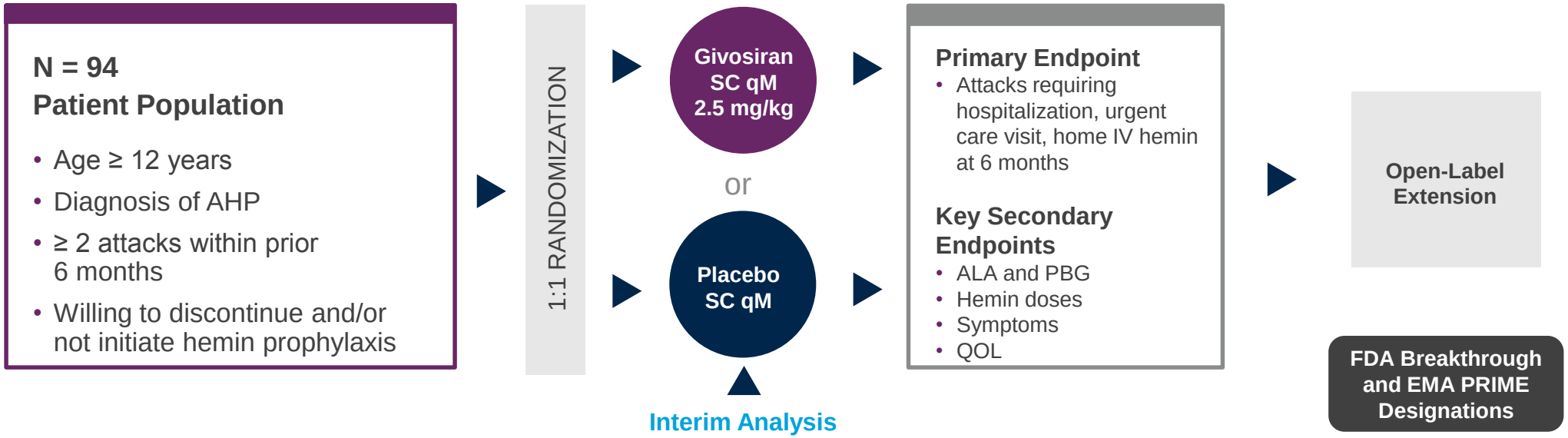


Data as of 7Jun2018; Anderson *et al*. AASLD Nov 2018. OLE: Open-label extension
Note: Duration between Phase 1 and OLE studies is not shown
†Attacks requiring hospitalization, urgent health care visit, or IV hemin at home.

ENVISION Phase 3 Study Design

Randomized, Double-Blind, Placebo-Controlled Study in Acute Hepatic Porphyria Patients

Enrollment completed – 94 AHP patients, 36 sites, 18 countries



Statistical Considerations:

- N = 70 patients results in at least 90% power to detect 45% reduction in annualized attack rate at 2-sided alpha of 0.05

ENVISION Interim Results*

Interim Efficacy Analysis & Safety

Interim analysis cohort

- N = 43 AHP patients (41 AIP; 1 VP; 1 HCP)
  - 23 randomized to givosiran; 20 randomized to placebo
- Treatment period: ≥3 months

Interim efficacy analysis (ALA levels at 3 months in AIP patients)

- Statistically significant reduction in urinary ALA, relative to placebo ($p < 0.001$)

Safety

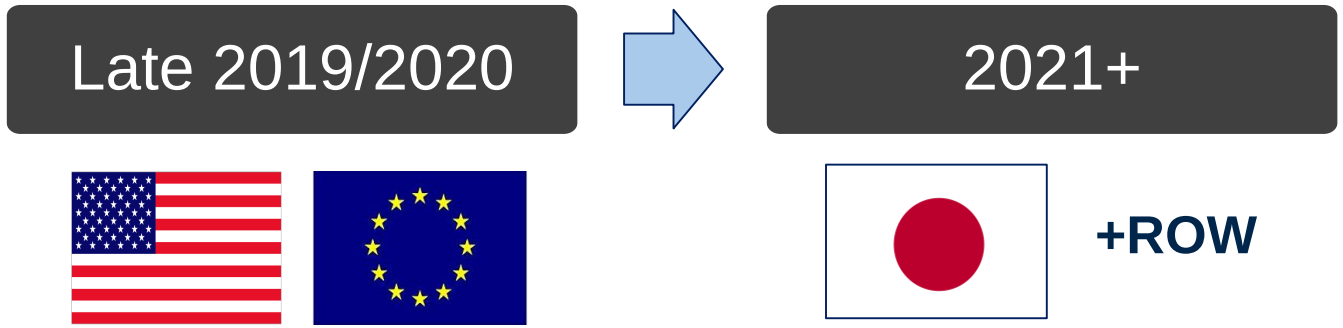
- No deaths
- Serious Adverse Events (SAE) reported in:
  - 5/23 (22%) of patients on givosiran
  - 2/20 (10%) of patients on placebo
- One patient (4%) on givosiran discontinued treatment based on a protocol-defined stopping rule due to >8x ULN increase in liver transaminase, which resolved
- No treatment discontinuations in placebo group

* Data cut-off date of 22Aug2018

Alnylam PHARMACEUTICALS

Program Status and Planned Timeline

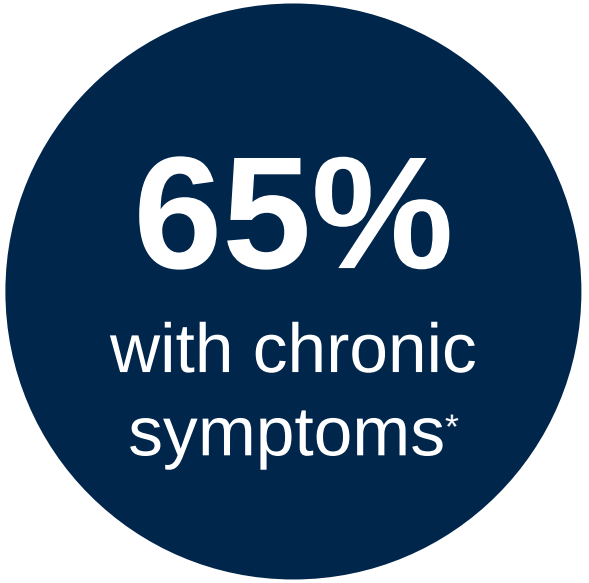
- ENVISION Phase 3 study in patients with AHP is ongoing
- Decision to file with 6-month data from ENVISION study to seek full approval
- Topline results from complete ENVISION study in early 2019
- Rolling NDA submission initiated, with addition of full clinical results in mid-2019; MAA submission in mid-2019
- Anticipated approval timelines*



* Assuming positive results and regulatory decision

AHP Patient Population

- Predominantly female
- ~5,000 patients with sporadic and 1,000 with recurrent attacks in U.S./EU



- Most commonly includes pain, tiredness, anxiety, and nausea

- AHP challenging to diagnose, and most patients currently remain undiagnosed
  - Low awareness, highly variable, with constellation of non-specific symptoms

†Anderson KE, Metabolic & Molecular Bases of Inherited Disease, 2001
‡ORPHANET; The Porphyria Consortium
*Data as of 11Apr2017

Alnylam PHARMACEUTICALS

Significant Economic Burden of AHP

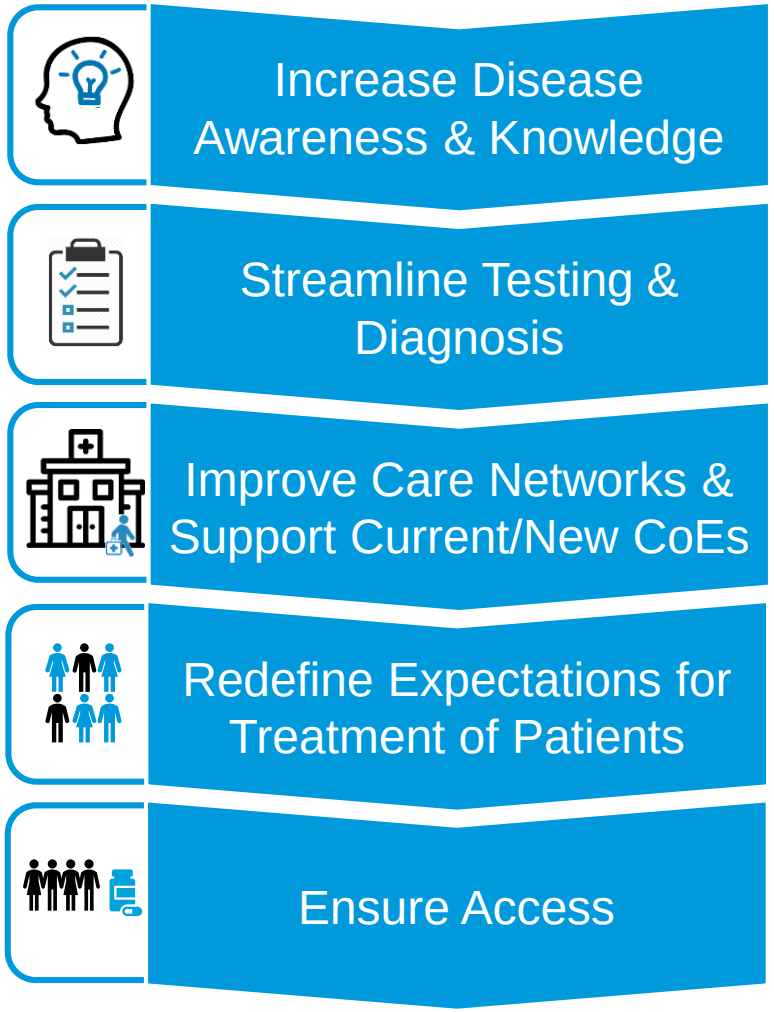
Healthcare Utilization and Cost Analysis in Recurrent Attack Patients*

Healthcare Utilization Category	Average Annual Cost Per Patient
Primary Care Physician Visit	$443
Specialist Visit	$1,203
Emergency Room Visits	$3,753
Hospitalizations	
Costs	$100,078
Charges	$356,853
Hemin Prophylaxis	$148,145
Hemin Acute Attacks	$141,738
Hemin Administration	$3,282
Total with Hospital Costs, mean (95% CI)	**$398,463 ($328,303 - $475,477)**
Total with Hospital Charges, mean (95% CI)	**$655,418 ($482,278 - $847,448)**

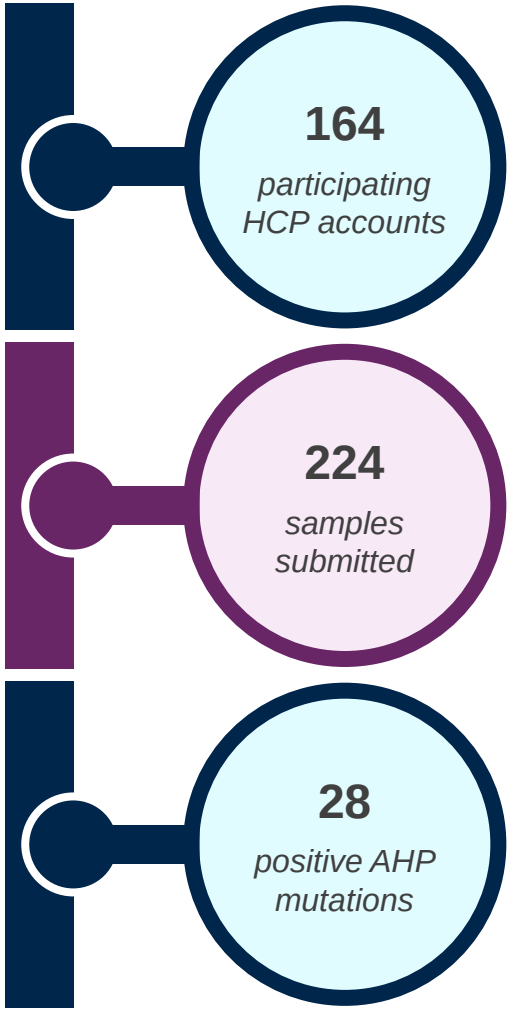
*EXPLORE Natural History study (Includes patients with ≥3 attacks per year). Annual expenditure per patient; based on both hospitalization charges (amount billed) and costs (amount paid) from published data sources in the US

Alnylam PHARMACEUTICALS

Facilitating Patient Identification and Improving Patient Care



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



Reduce barriers to genetic testing and counseling

Tests and services are performed by independent third parties

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

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

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

At no time does Alnylam receive patient-identifiable information. Alnylam receives contact information for healthcare professionals who use this program
Results as of November 28, 2018

Reaching an Enriched Audience via Social Media

Pilot Effort with Facebook Communities Ongoing

Target Specific FB Communities

- Target Audiences served ads on FB
- Clicks directed to online health survey

Enrich Audience

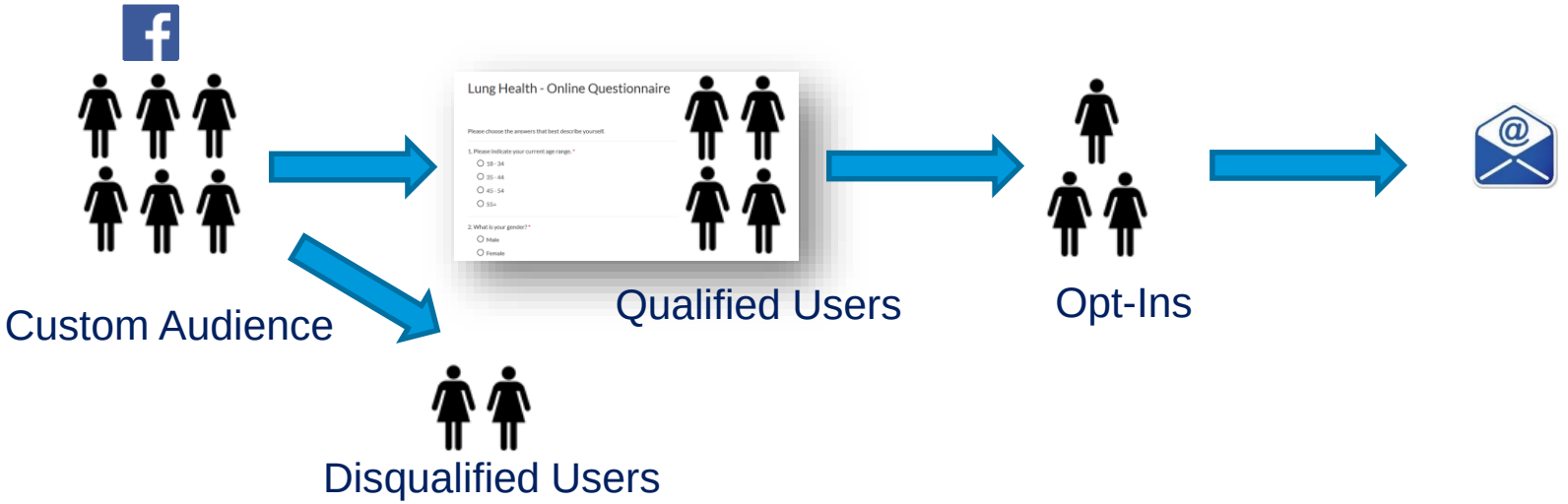
- Responses to survey identify potential AHP patients

Users Opt-In to be Contacted

- Respondents opt-in to share contact details and receive further information about AHPs

Disease Information Delivered

- Opt-In patients receive information

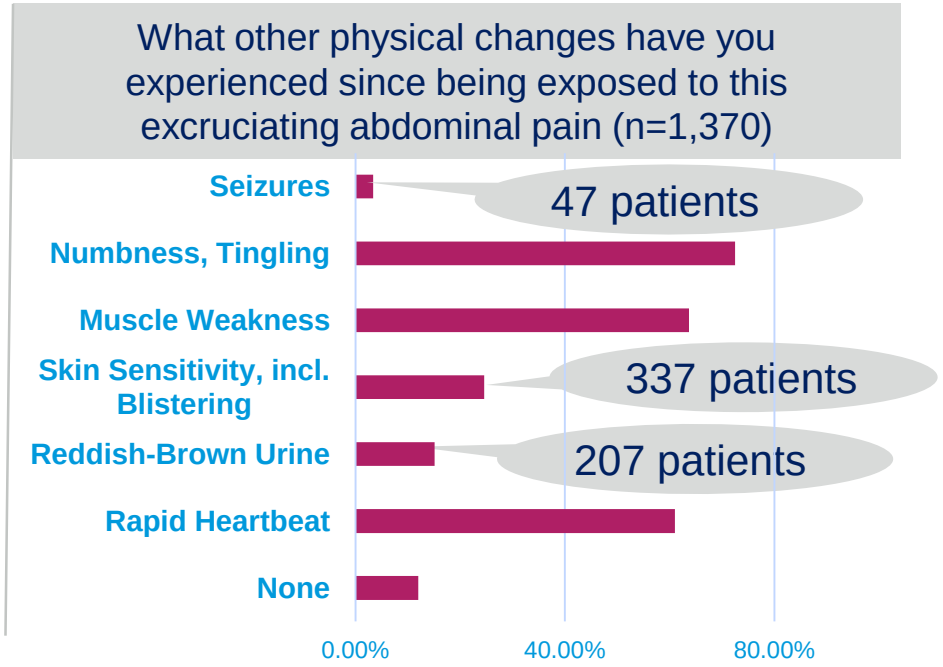


Reaching an Enriched Audience via Social Media

Initial Results After 4 Weeks*

Approximately 11,600 respondents; 400+ have answered all questions

- 72% have intense abdominal pain that can last hours at a time
  - 95% mentioned it reoccurred without proper diagnosis or treatment
  - 65% with constipation, 80% with nausea, 35% with vomiting



Demographics

- 98% female (72% 34-54)
- 22 have been diagnosed with or tested for porphyria
- 19 have family members diagnosed with porphyria

~1,300 respondents signed up for future information about AHP

*Initial results may not represent future results. Results are based on de-identified respondent survey data.

Givosiran Market Opportunity

Givosiran has potential to address significant unmet needs

- Current treatment options inadequate
- 65% of recurrent attack patients have chronic symptoms during and between attacks
  - Opportunity to expand to sporadic attacks and chronic manifestations

Significant economic burden

- Average annual expenditure for patients with recurrent attacks ranging from approximately $400,000 to $650,000

Disease significantly under-diagnosed

- Estimated disease prevalence (2-5:100,000) suggests only ~20% of patients currently diagnosed
- Often misdiagnosed, with delays in diagnosis up to 15 years

Education efforts underway to drive improved awareness and diagnosis

- Primary focus on gastroenterologists, neurologists, hematologists
- Partnerships with patient advocacy groups

Q&A Session #1

10:00 – 10:30

Moderator:

- Yvonne Greenstreet, MBChB, Chief Operating Officer

Panelists:

- Eric Green, VP & General Manager, TTR Program
- Pushkal Garg, M.D., Chief Medical Officer
- Andy Orth, SVP, Head of U.S. Business
- John D. Phillips, Ph.D., University of Utah
- Akin Akinc, Ph.D., VP & General Manager, Givosiran

Break

Presentations to Resume at 10:45am

Primary Hyperoxaluria Type 1 & Lumasiran

Sally-Anne Hulton, M.D., Birmingham Children's Hospital NHS Trust

Pritesh Gandhi, PharmD., VP & General Manager, Lumasiran

Alnylam® PHARMACEUTICALS

Primary Hyperoxaluria

Sally-Anne Hulton

Consultant Paediatric Nephrologist

Birmingham

UK

Consulting Disclosures:
Alnylam
Dicerna
Chiesi

Birmingham Women's and Children's NHS
NHS Foundation Trust

Enzyme deficiency in the liver targets the kidneys

AGT enzyme defect in the liver → ↑ oxalate production

Kidneys normally excrete oxalate

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

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

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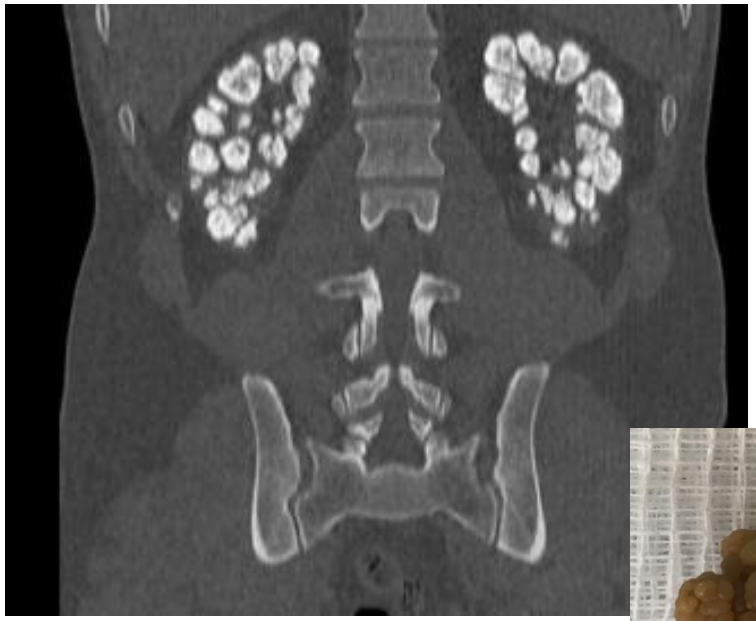
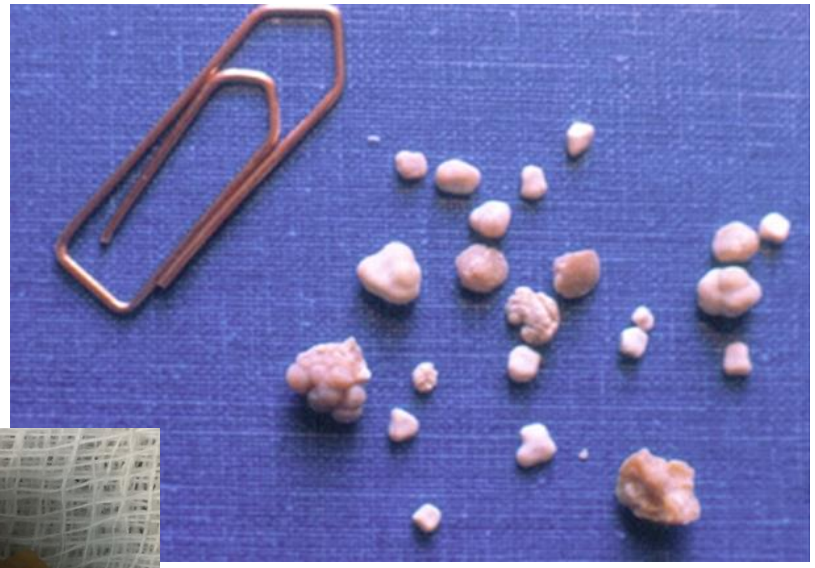
Clinical presentation & diagnosis

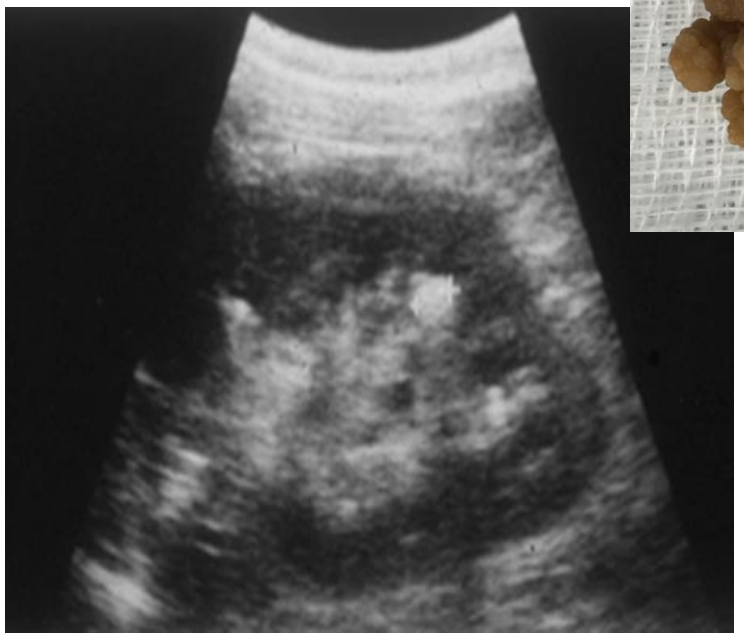
asymptomatic → stones single or recurrent → nephrocalcinosis → renal impairment

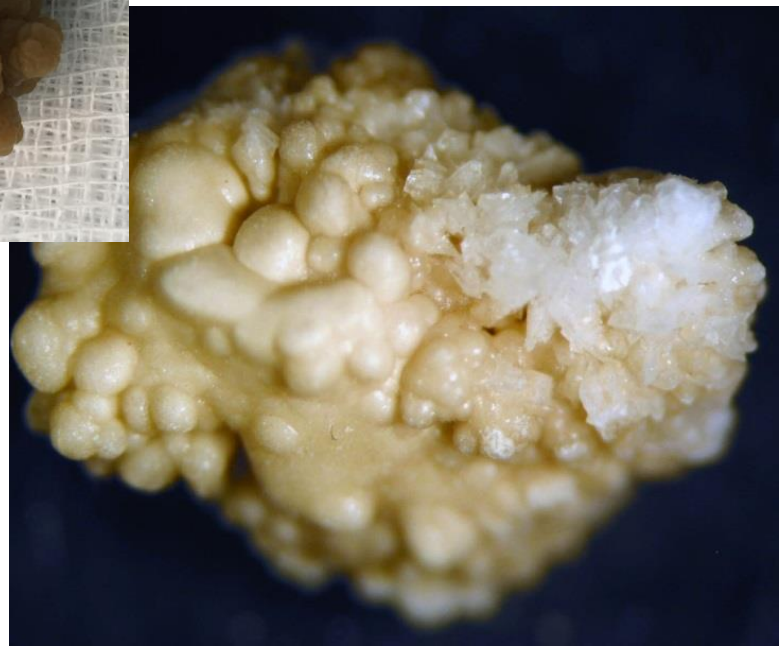
stones single or recurrent → Stone in urine → Stone to laboratory for analysis

Calcium Oxalate present → Specific blood and urine tests









122

OxalEurope: 23 countries with >1300 patients

PH1: incidence ≈ 1 per 100 000 live births

prevalence ≈1 to 3 per million

PH1: 1100
PH2: 110
PH3: 82

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

SF Garrelfs 2018

PH under diagnosed in Middle East and Asia

- Diagnosis often missed or delayed[4]
  - Lack of availability of diagnostic tools
  - Highly variable age of onset, presentation and progression

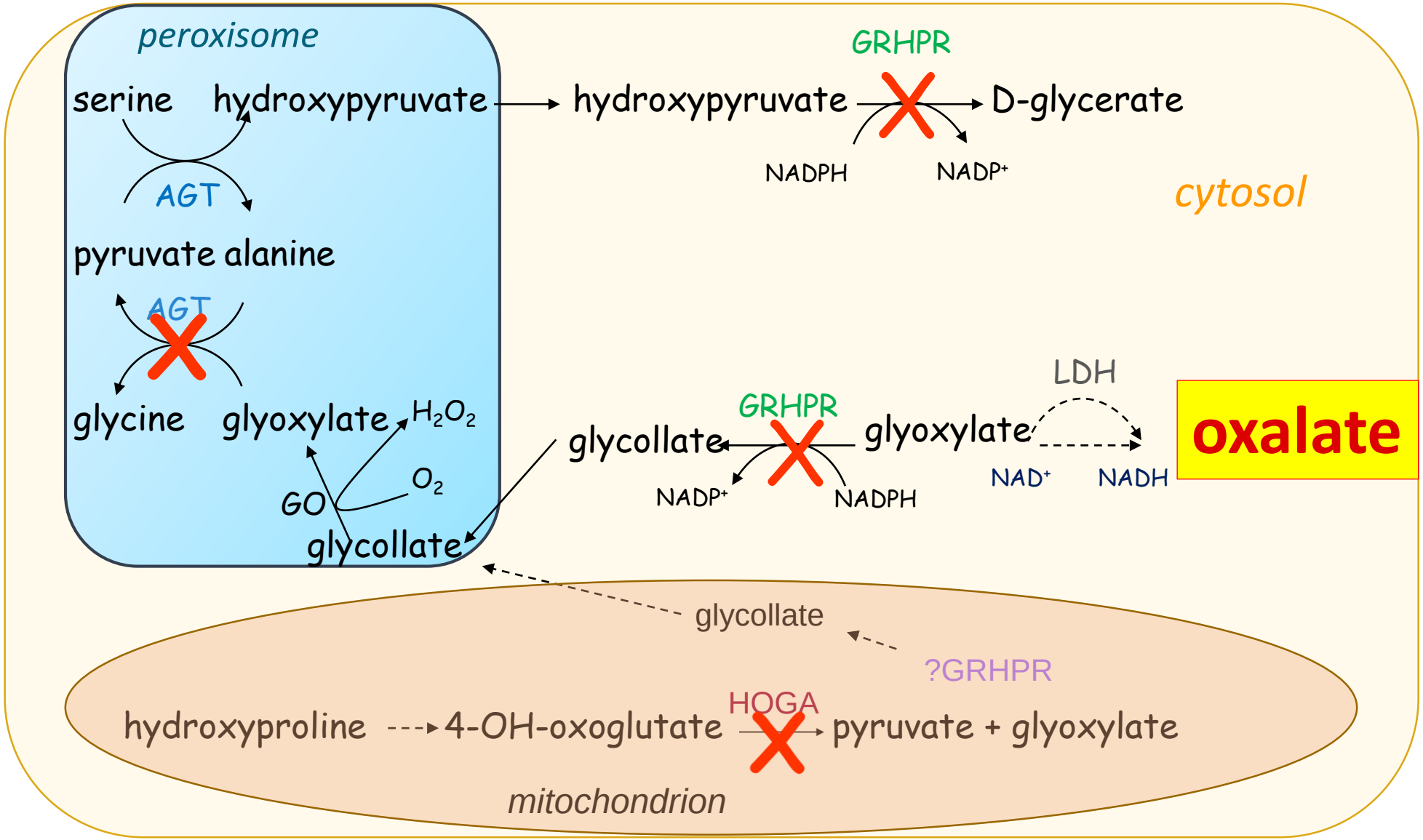
- ↑ U oxalate 24- 40% of Pakistani children with stones[1]. 150 PH1 Pakistani patients studied[2]

- Estimates of high disease burden: incidence of 1 in 14 500 (based on UK data[3]) with gene frequency ranges from 1 in 4000 to 200 000[4]
  (cf 1 in 200 000 in Europeans)

- Incidence:
  - Pakistan: 1 in 1000 - 50 000
  - Morocco: 1 in 27 500 - 32 000

[1]*Rizvi SA et al. Ind J Urol 2007: 23(4) 420-7*
[2]*Khaliq S et al. Abstract: Am Soc Hum Gen 2013*
[3]*Hutchesson AC et al. J Med Gen 1998;35(5) 366-70*
[4]*Talati JJ, Hulton SA et al. Urolith 2018;46 (2) 187-95*

Oxalate Synthesis

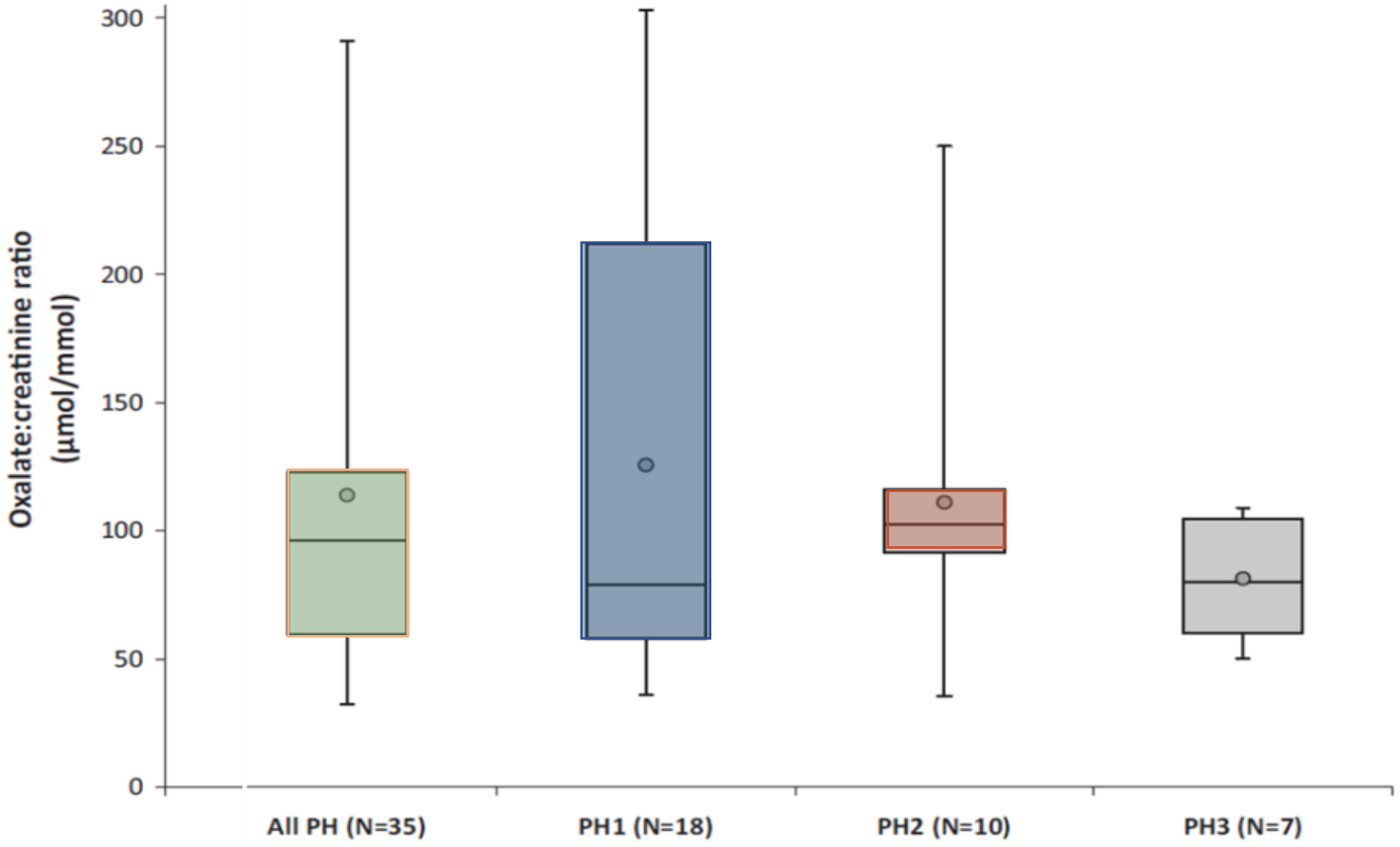


PH mutations & diagnosis

- **PH1 AGXT gene *chr 2***
  → plasma oxalate + glycollate
  → urine oxalate
- **PH2 GRHPR gene *chr 9***
  → urine L-glyceric acid
- **PH3 HOGA1 gene *chr10***
  → urine oxalate + glycollate

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

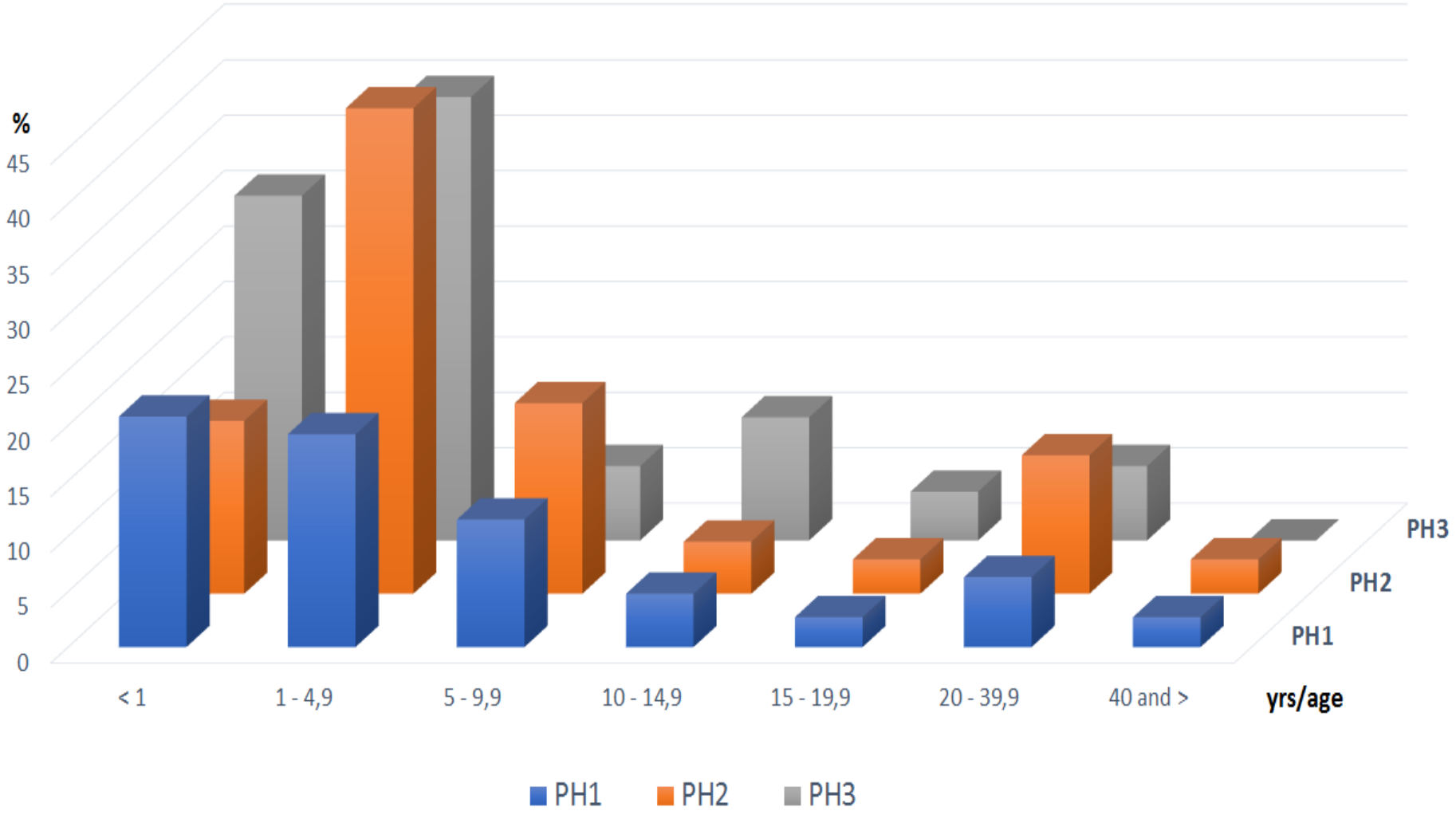
Urine oxalate excretion in PH illustrating overlap of urine oxalate/creatinine ratio



Box denotes interquartile range; whiskers the 2.5 and 97.5 centile

Rumsby G et al UCL laboratory 2018

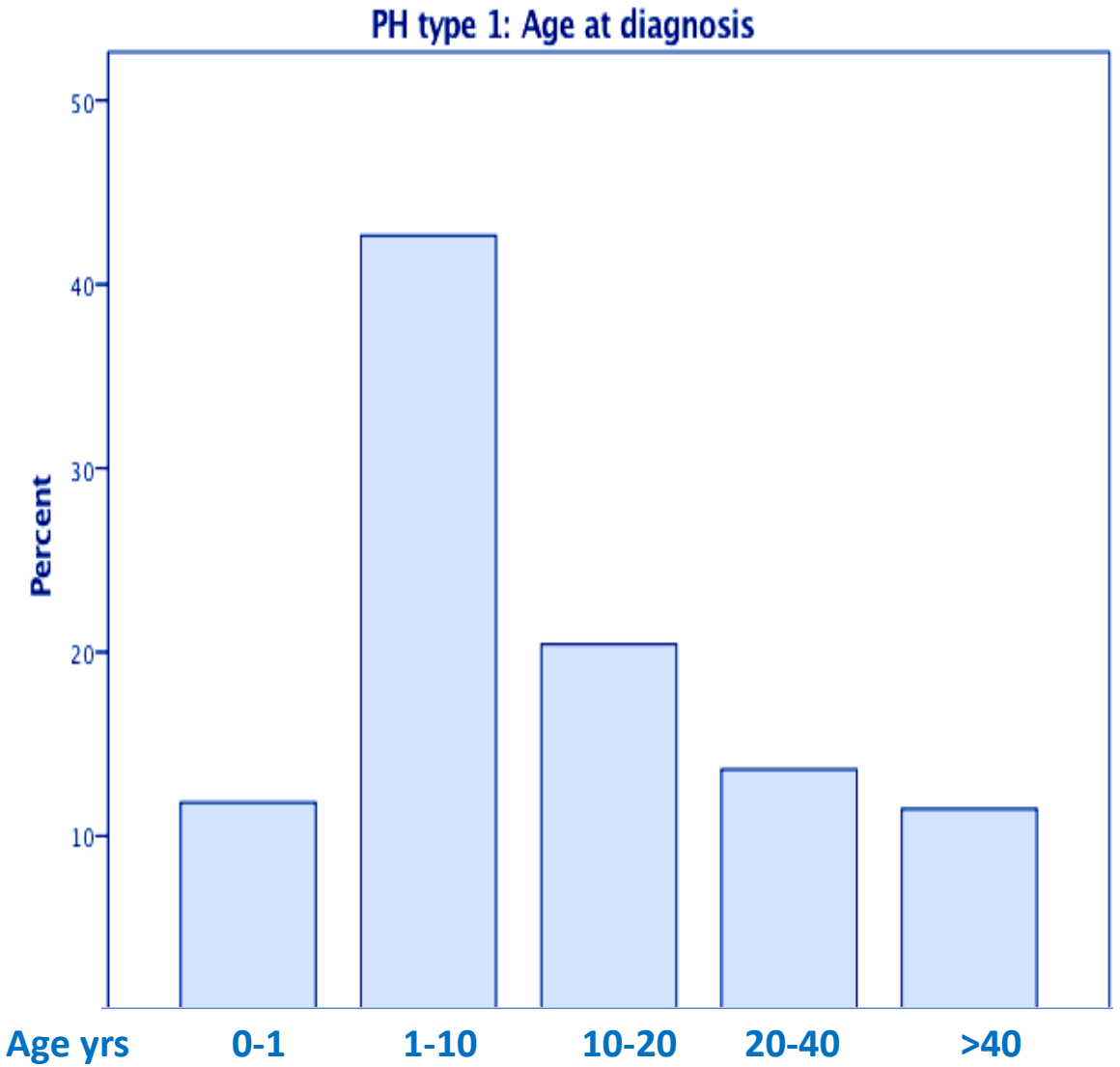
Age of onset: PH1, 2 and 3



SF Garrelfs on behalf of

OXALEUROPE

PH1: age at diagnosis n=297



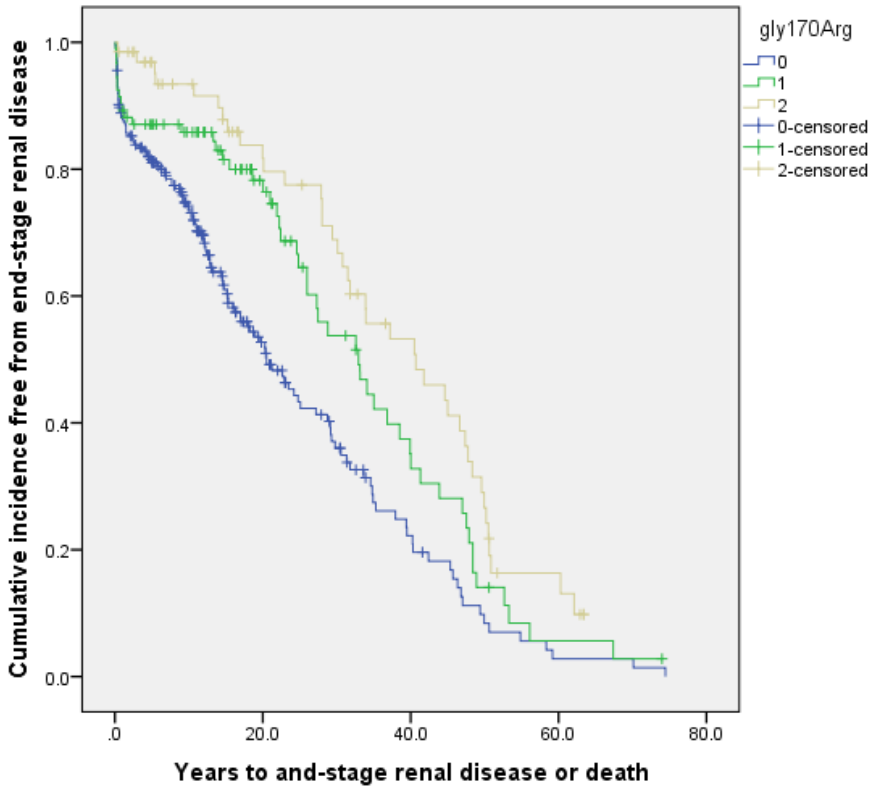
OXALEUROPE

Courtesy: S Garrelfs

Early genetic diagnosis relevant

- Affects long term outcome
- Some PH1 children stable GFR over 20yrs – have a specific genotype – sensitive to vitamin B6

Specific mutation

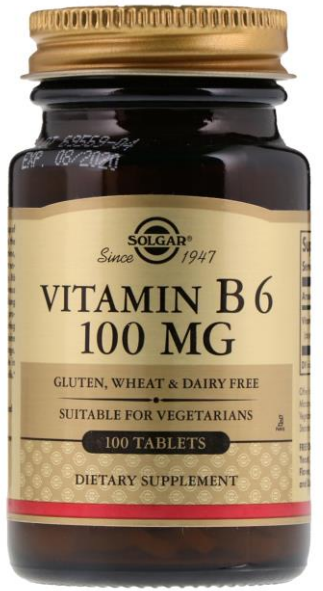


Fargue S et al KI 2009; 76: 767-73

Mandrile G et al, Kid Int. 2014: 86(6):1197-204

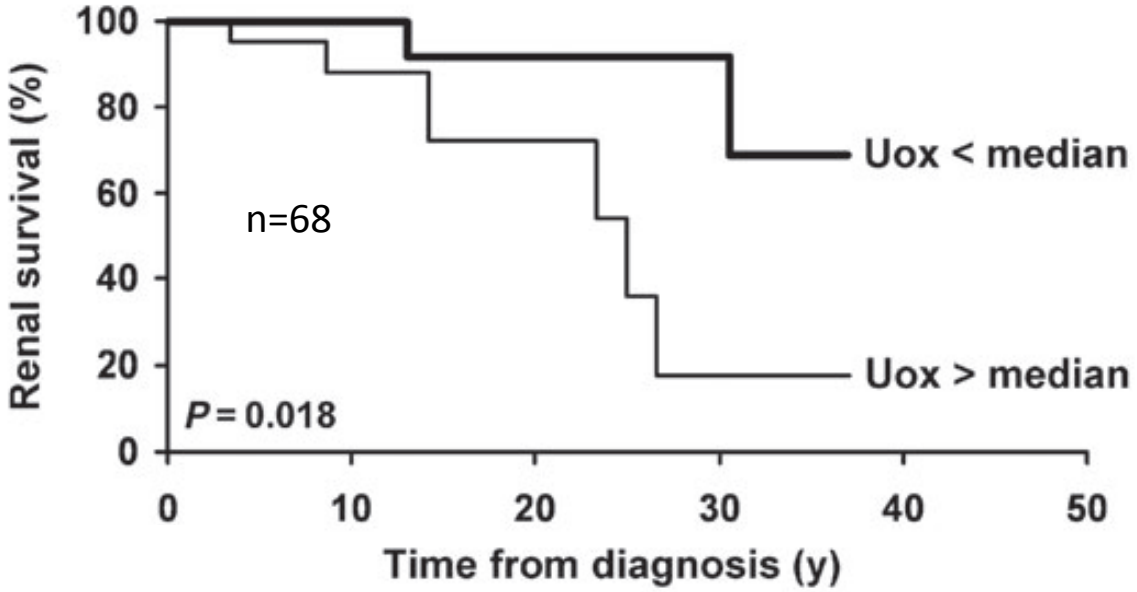
Standard treatment for PH1

- High fluid intake 2.5l/m^2/day min
- Vitamin B 6 (pyridoxine)
- Limit Vit C intake, oxalate containing foods



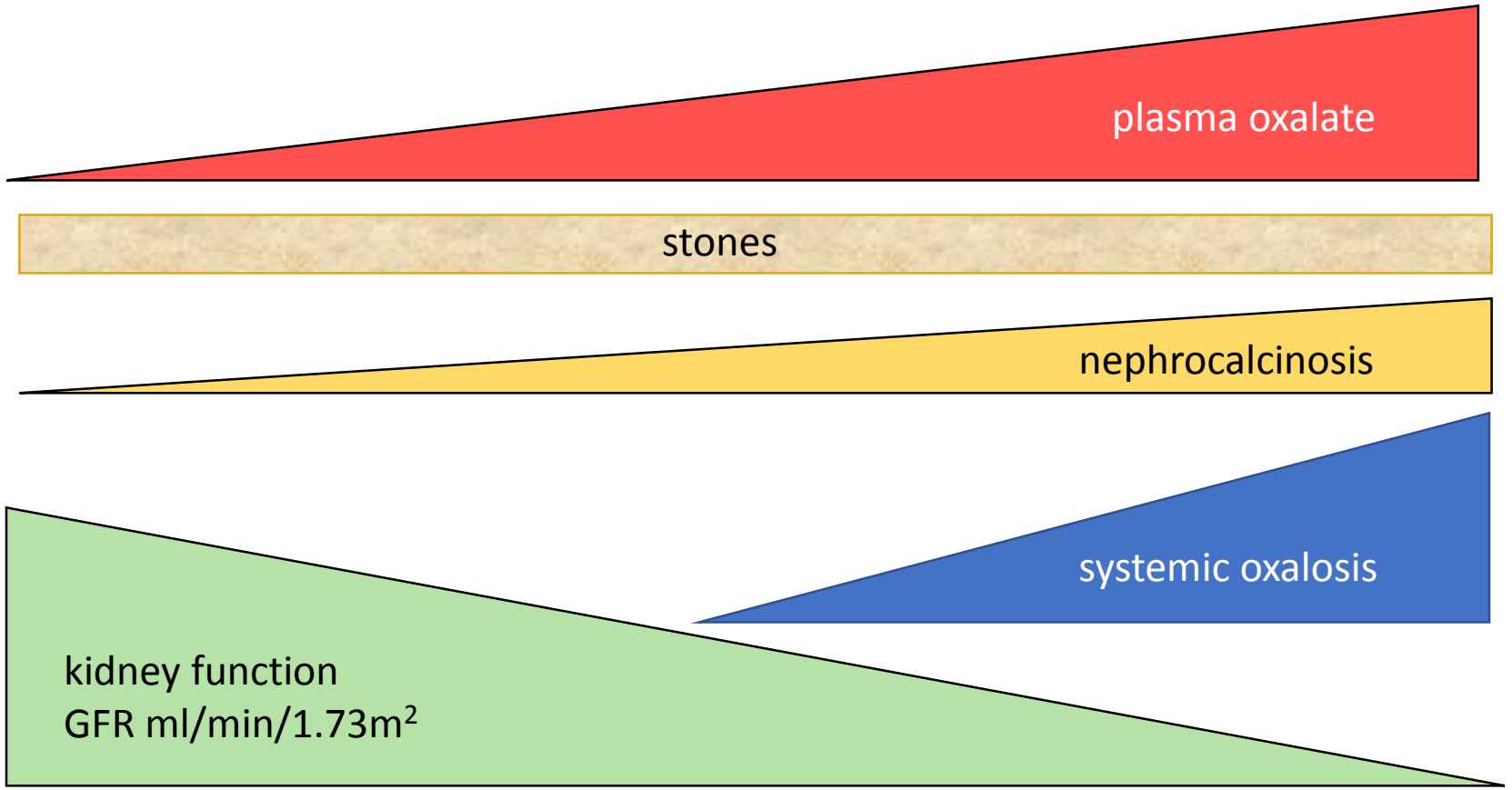
Factors impacting on kidney survival

- Degree of hyperoxaluria
- Nephrocalcinosis



Tang X et al. *Kid Int 2015: 87(3):623-31*

Progression of systemic oxalosis



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

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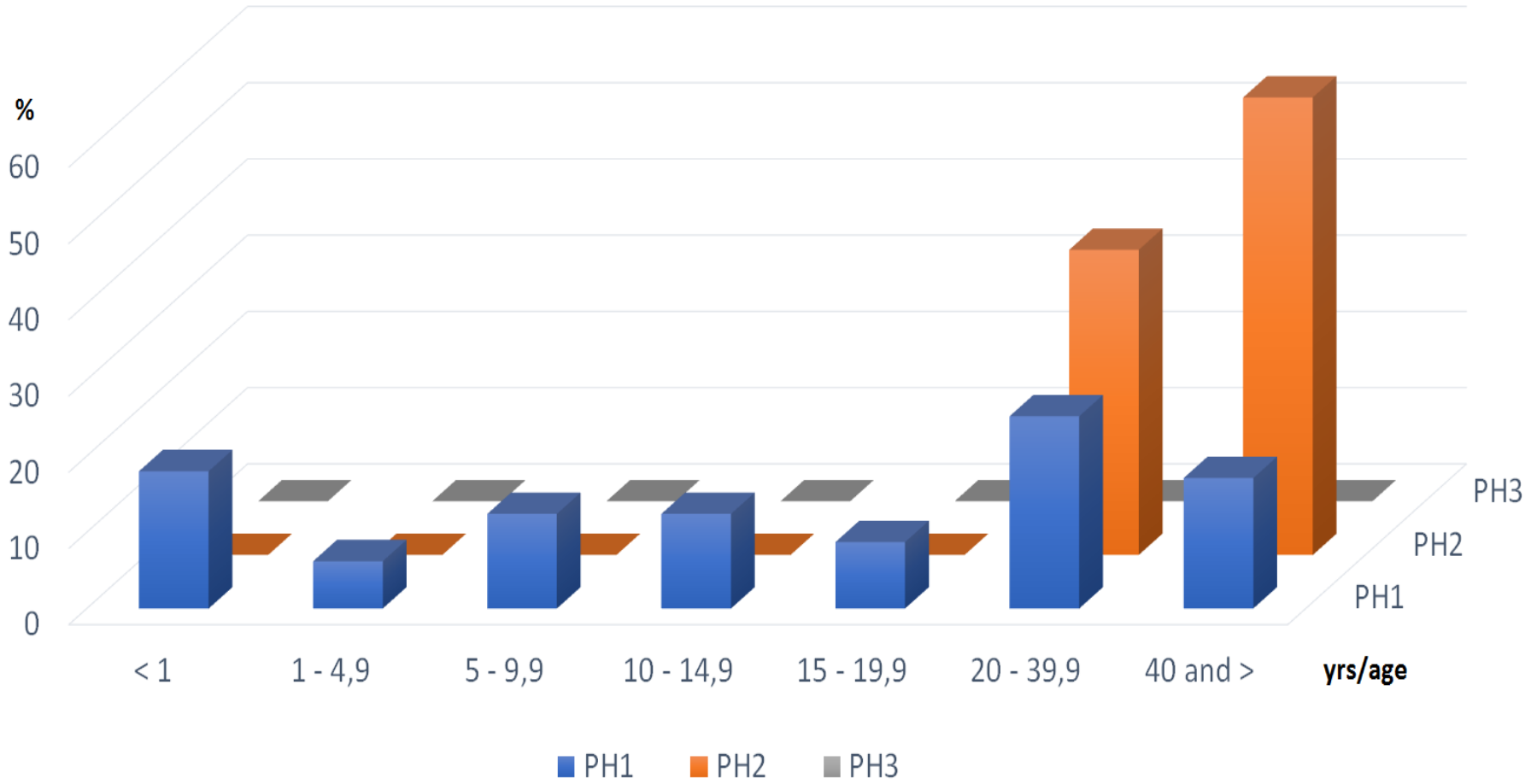
Age at time of kidney failure: PH1 vs PH2



SF Garrelfs on behalf of

OXALEUROPE

Kidney failure in childhood PH1

- Consanguineous families – high prevalence
- <1% of paediatric ESRD in USA, UK[1], Japan[2]
- 10 % for Kuwait[3]
- 13% for Tunisia[4]

[1] *NAPRTCS and UK Renal Registry Annual Reports*
[2] *Ped Nephrol 2002,17 (6) 456–61*
[3] *Transpl Proc 2004, 36 (6) 1788–91*
[4] *Ped Nephrol 1996, 10, (4) 479–82*

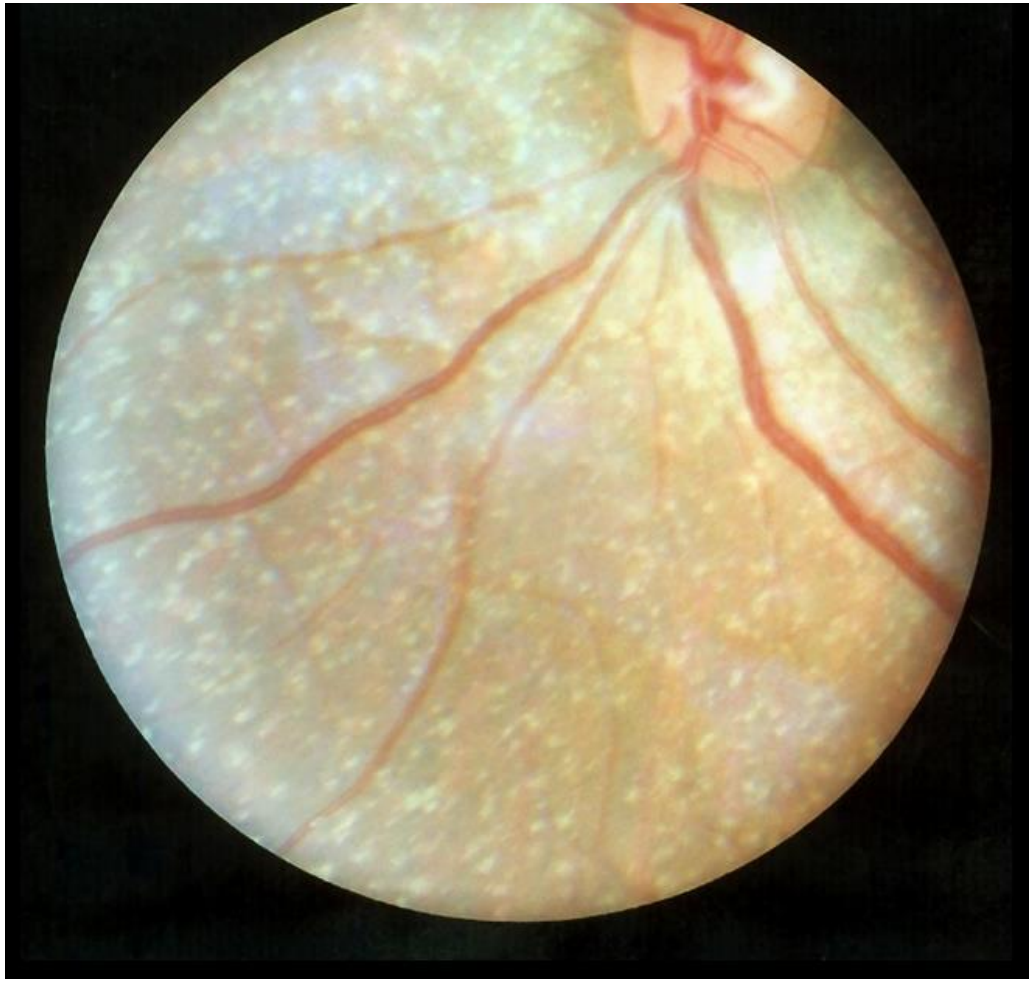
Consequences of PH1

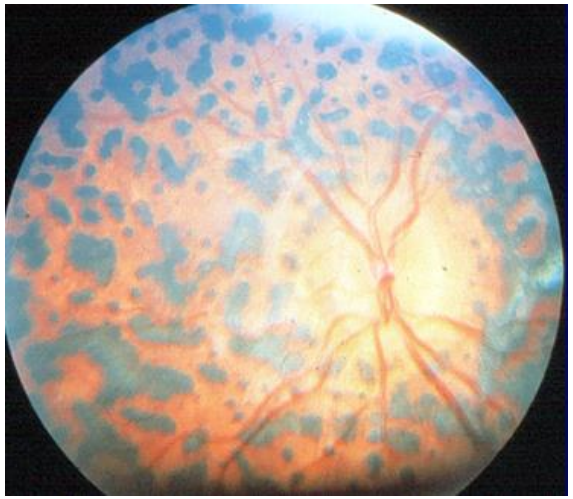
- Variability in presentation
- Progressive decline in kidney function
- Systemic deposition of Ox in all organs
  - bones
  - heart
  - skin
  - bone marrow: anaemia
  - eyes: retinal damage
  - neurological

51 of 132 PH1 patients
→ systemic oxalosis[1]

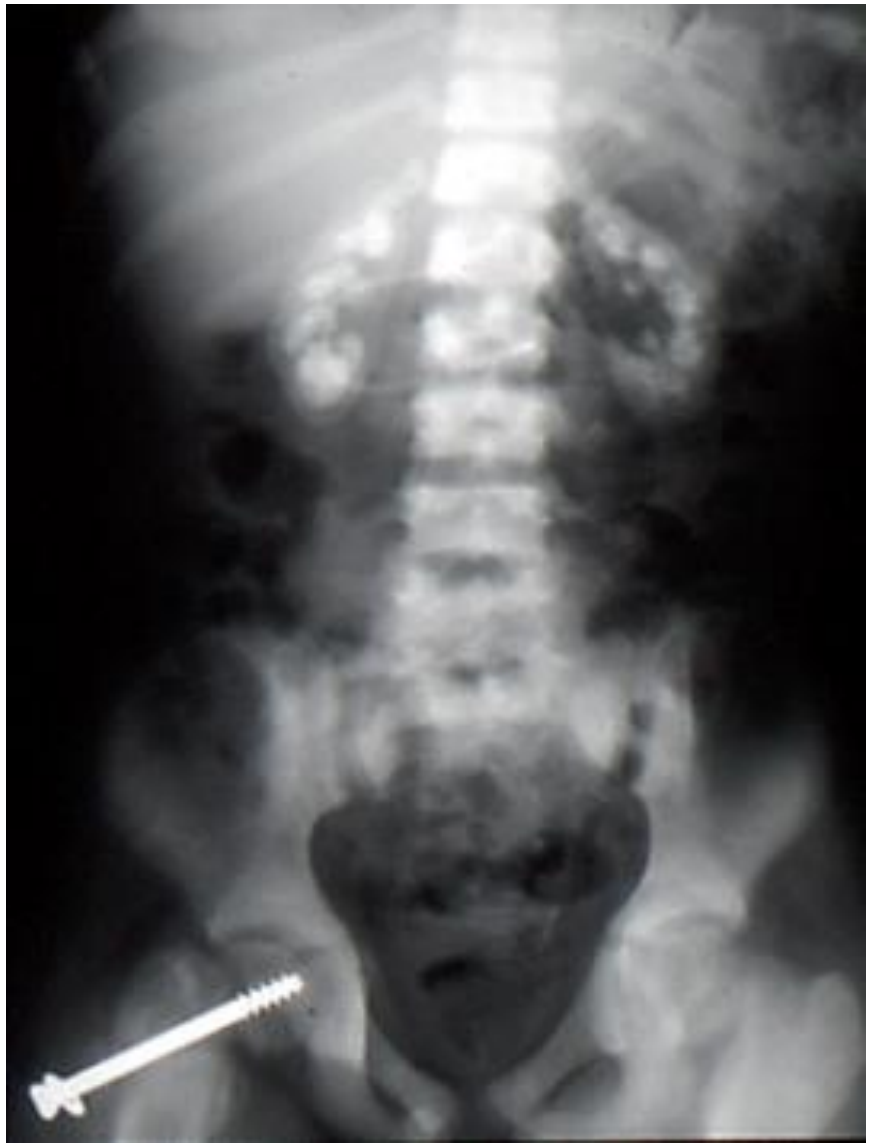
[1]*Garrelfs S et al. On behalf of OxalEurope; IPNA 2016*

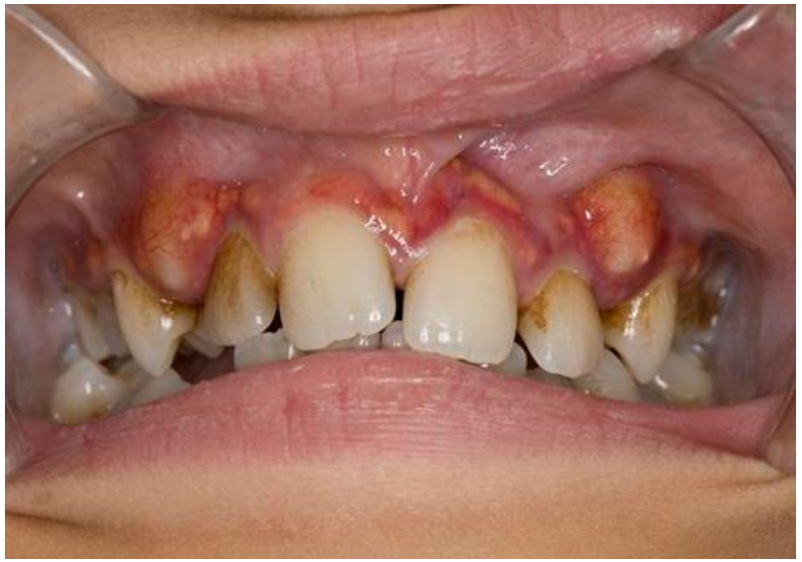
Consequences of systemic oxalosis

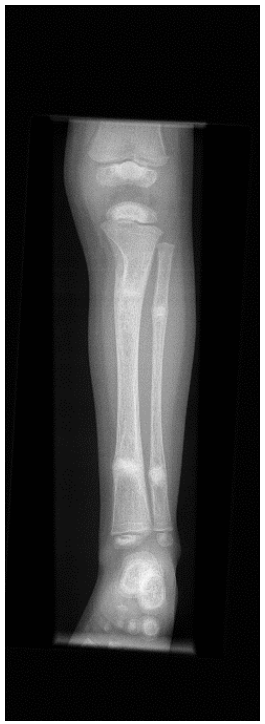


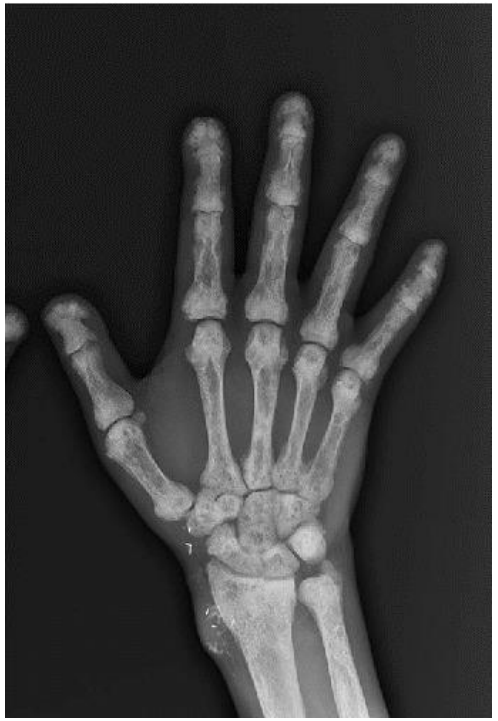


Oxalate crystals on fundoscopy and in retina on post mortem









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

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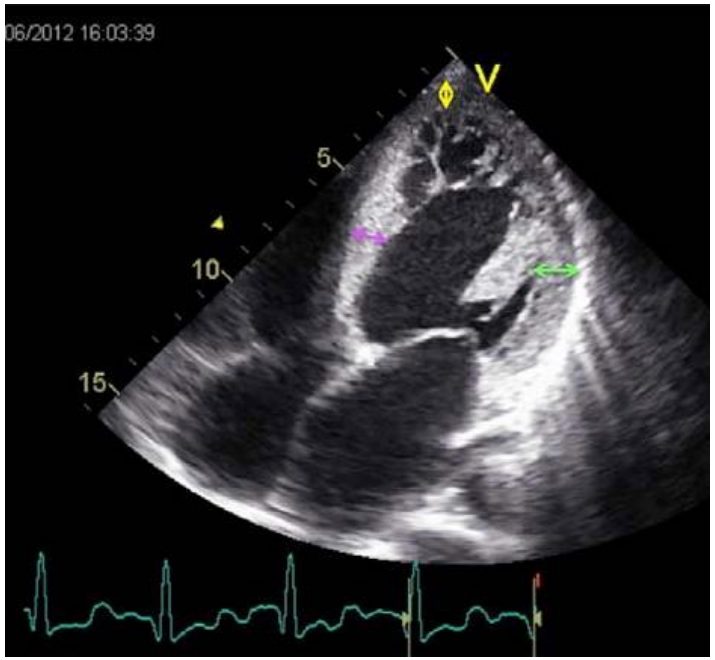
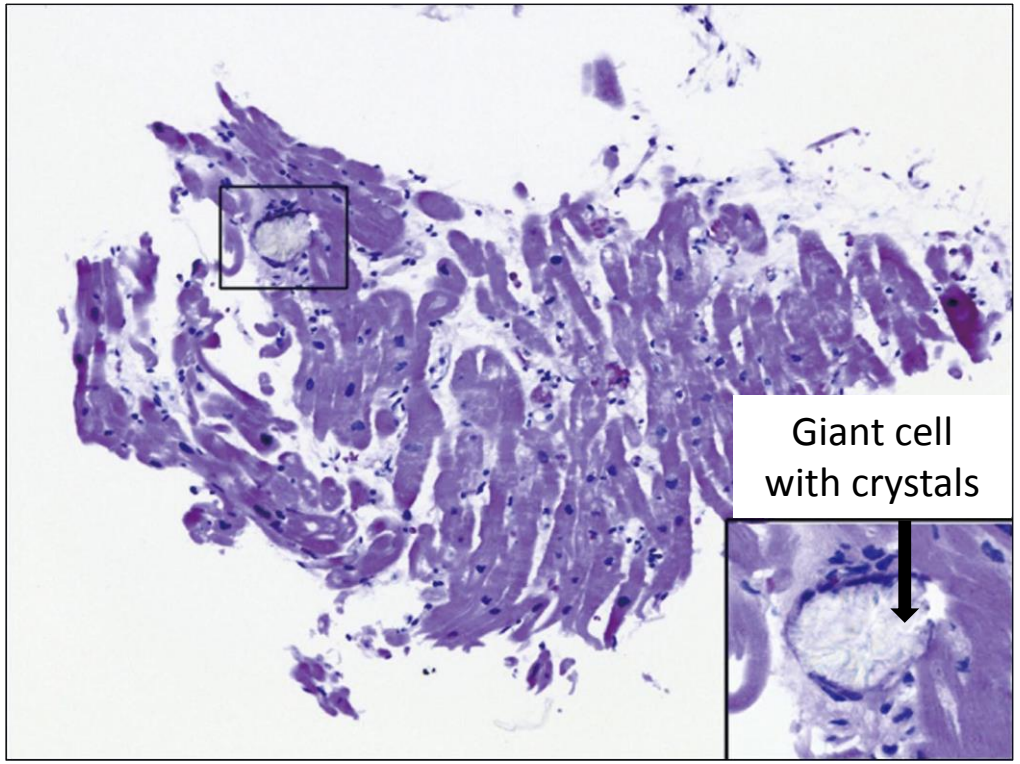
Consequences of PH1



Cardiac echo showing increased wall thickness

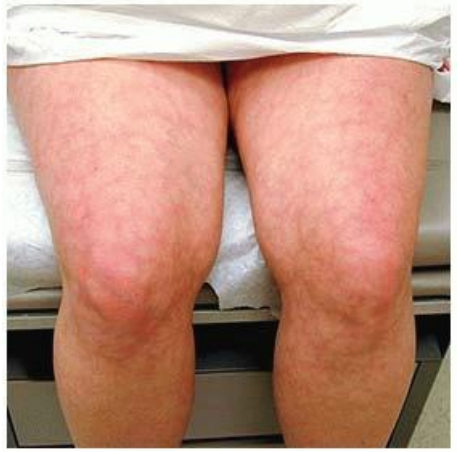
CR Lagies et al: Circ Heart Fail 2013;6: e45-7

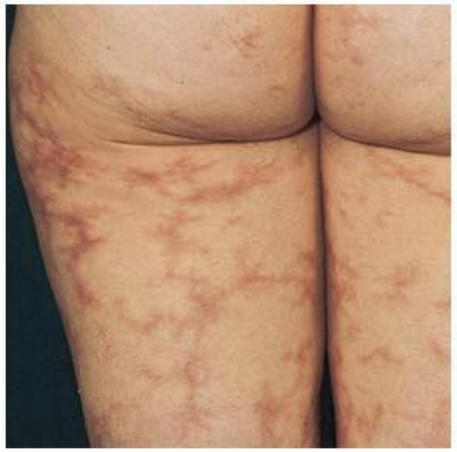
Endomyocardial biopsy right ventricle



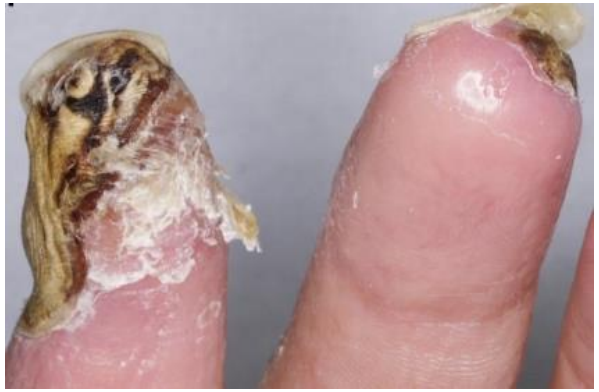
F Mookadam et al: Circ J 2010; 74: 2403 – 2409

Consequences of PH1

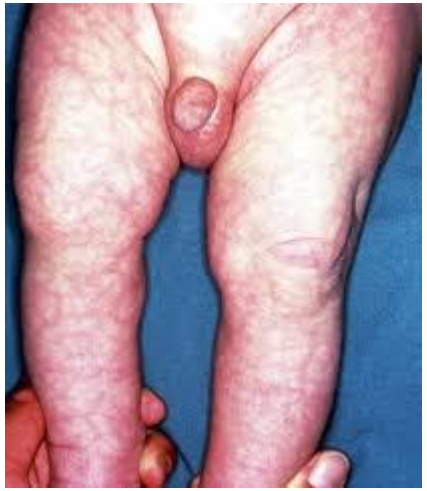


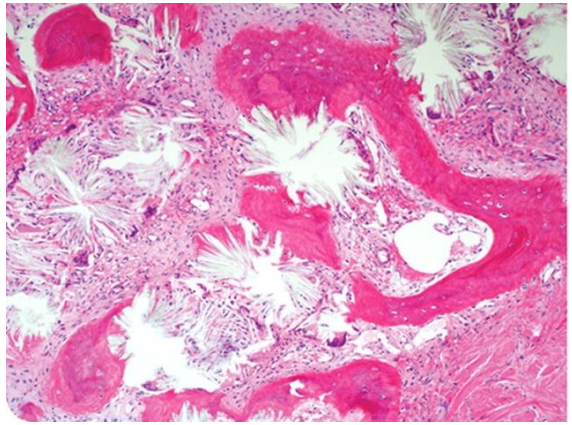


Livedo reticularis of skin



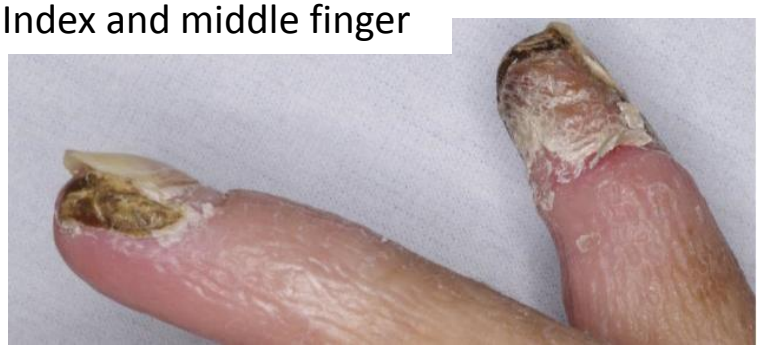
Gangrene of fingers with osteolysis in secondary oxalosis





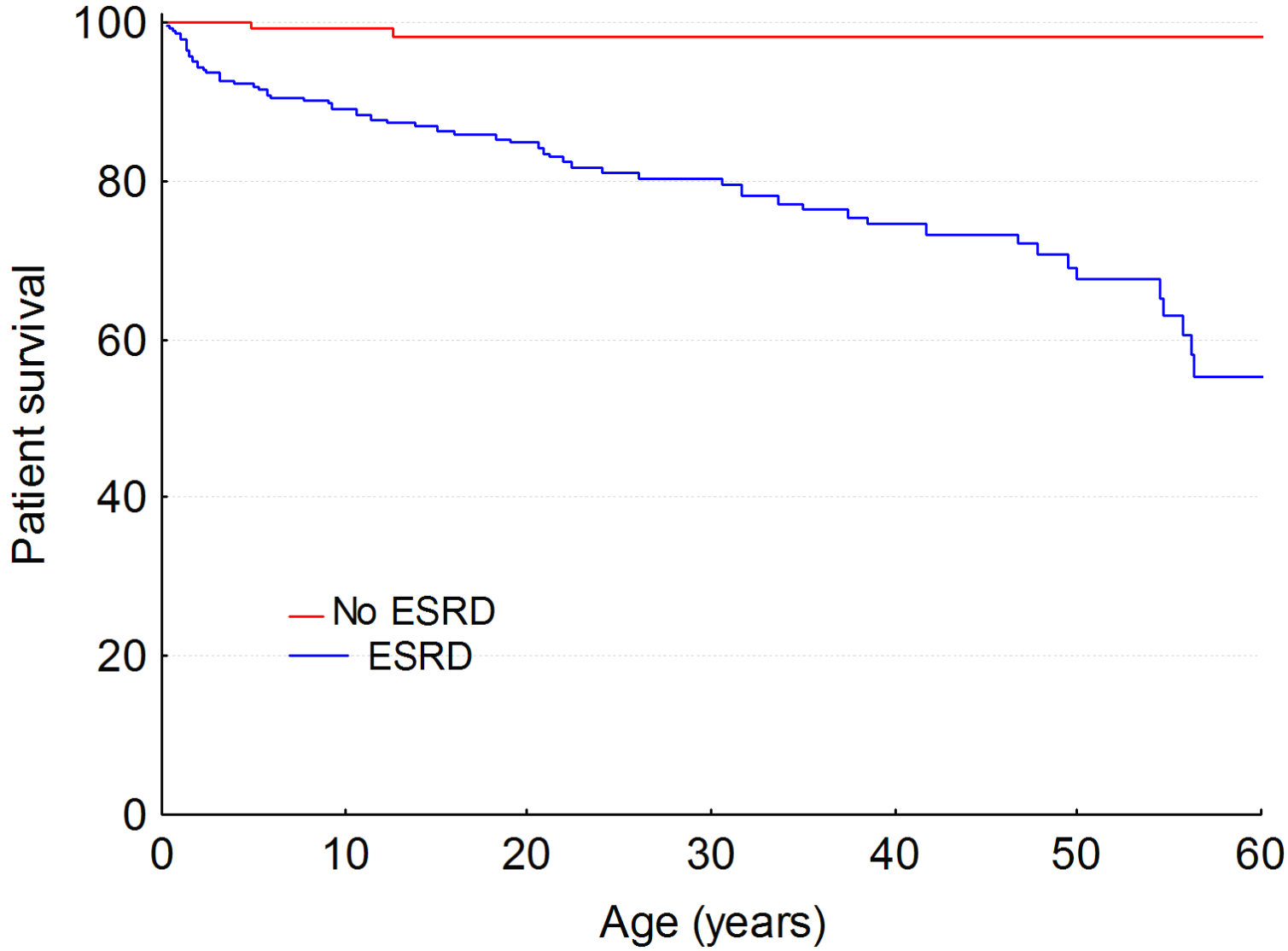
Crystals in bone marrow

Index and middle finger



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

Patient survival PH1: importance of ESRD



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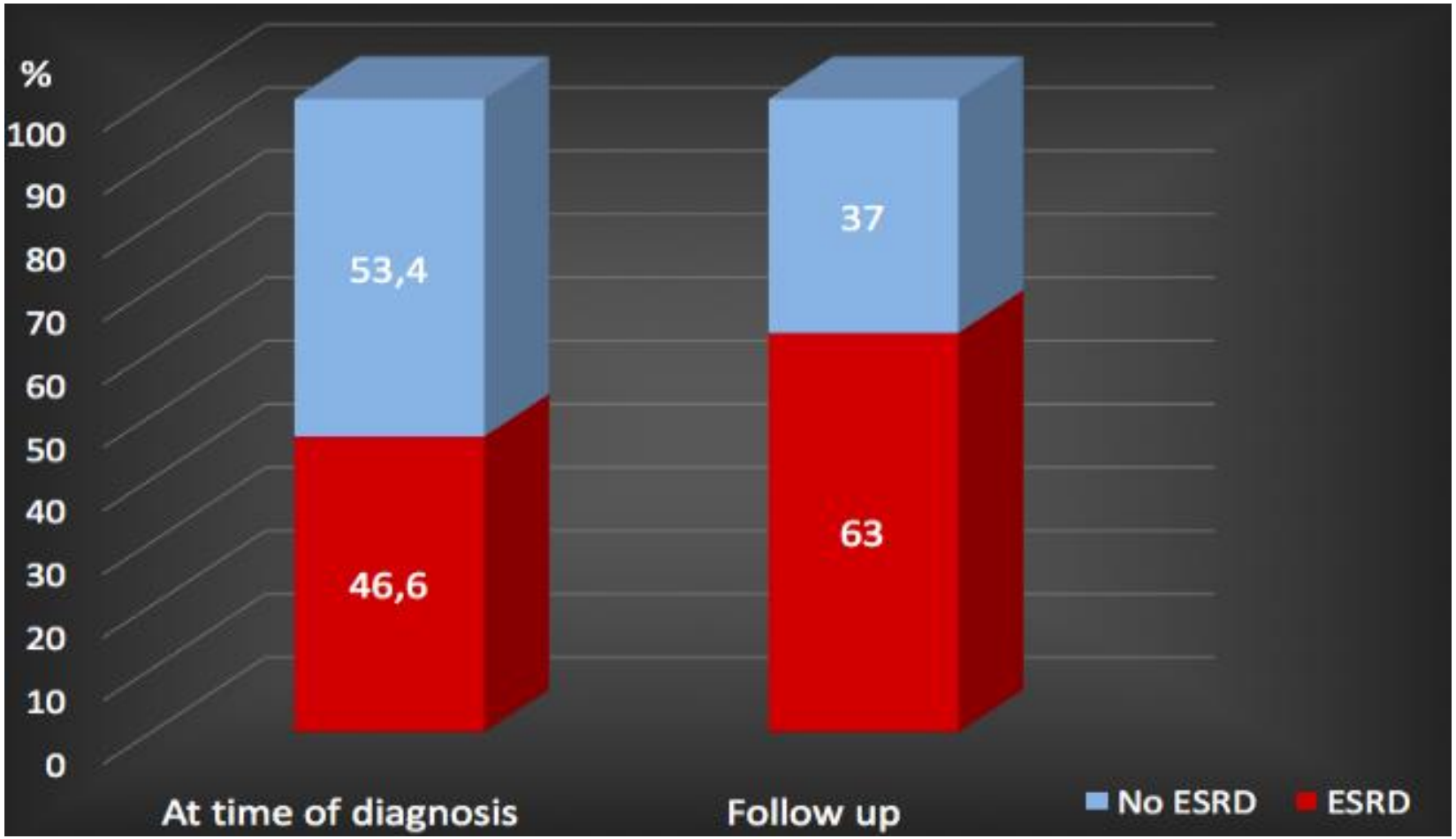
OXALEUROPE

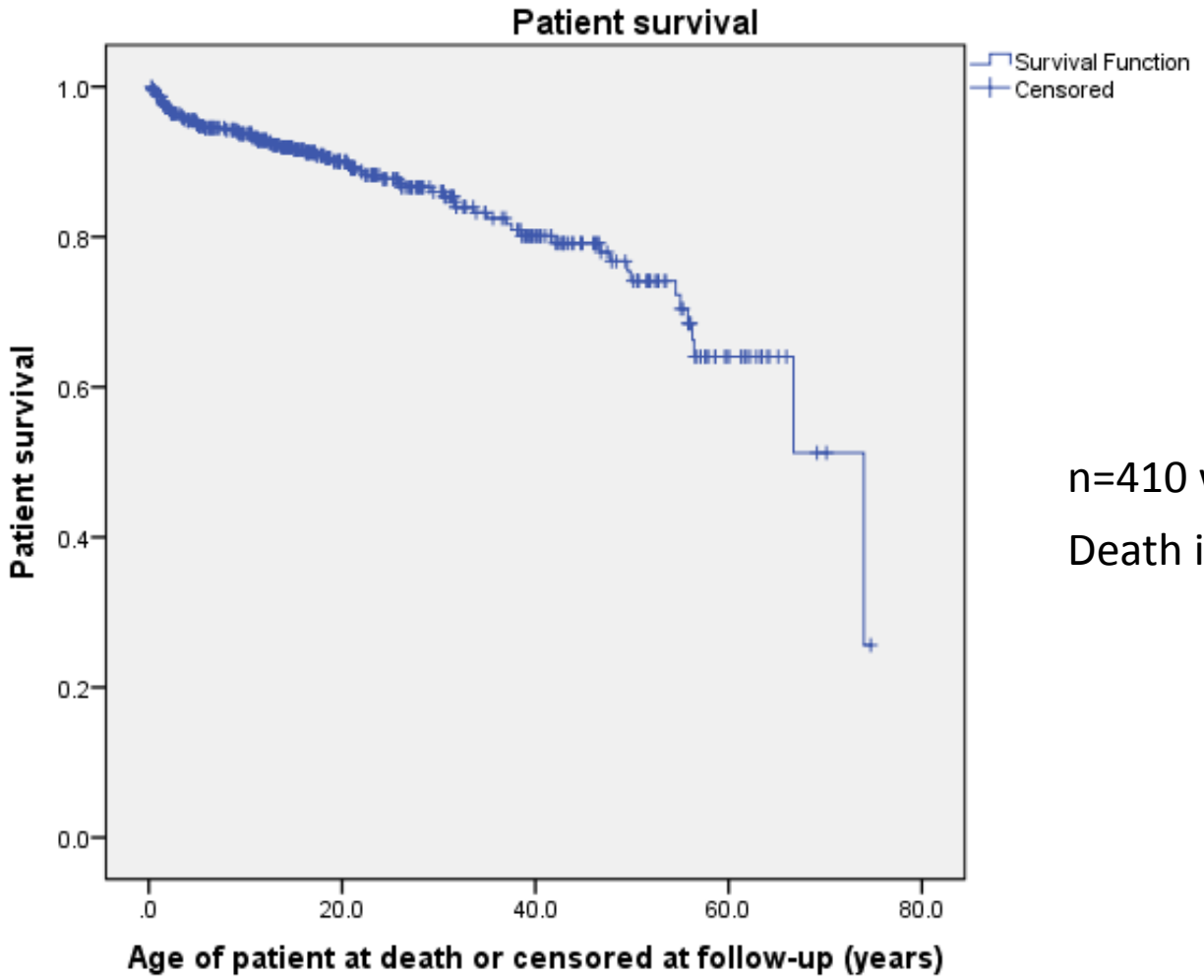
Kidney failure – PH1



End Stage Renal Disease at time of diagnosis
< 18 years (34 %) > 18 years (74 %)

SF Garrelfs for
OXALEUROPE

PH1 patient survival curve



n=410 with full AGXT genotype

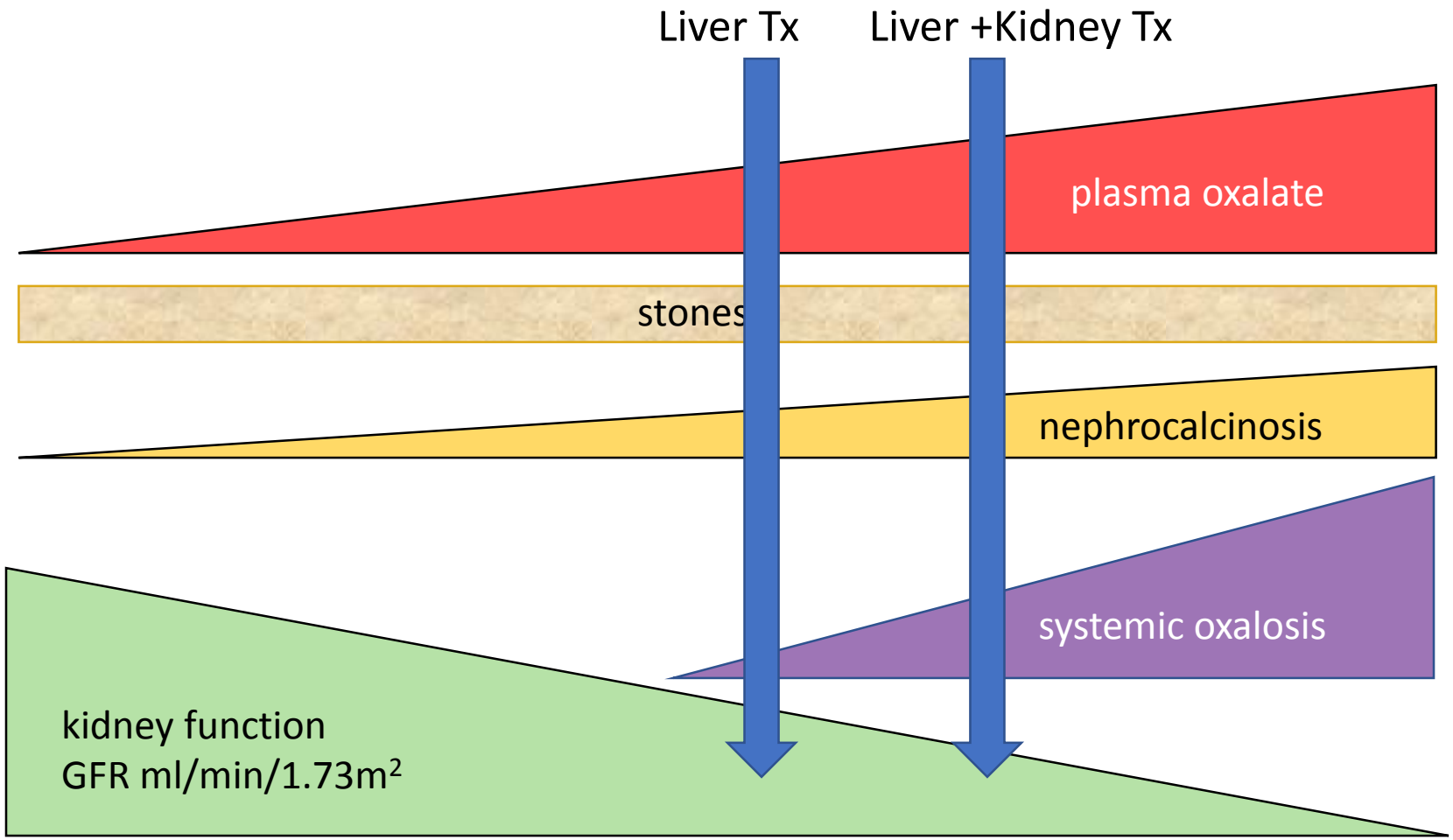
Death in 13%

Mandrile G et al. Kid Int. 2014; 86(6):1197-204

Infantile Systemic Oxalosis PH1

- Prognosis poor
- Early death is common
  - 50% have ESRD at diagnosis and 80% develop ESRD by 3 years[1]
- Only effective treatment options are early combined liver + kidney transplantation or isolated liver transplant + dialysis

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



CKD stage 1 **> 90**	**CKD stage 2** **60 - 89**	**CKD stage 3** **30 -59**	**CKD stage 4** **15-29**	**CKD stage 5** **<15**
Good renal function ±↑ Uox	Mild impairment	Moderate impairment	Progressive decline	End stage renal disease

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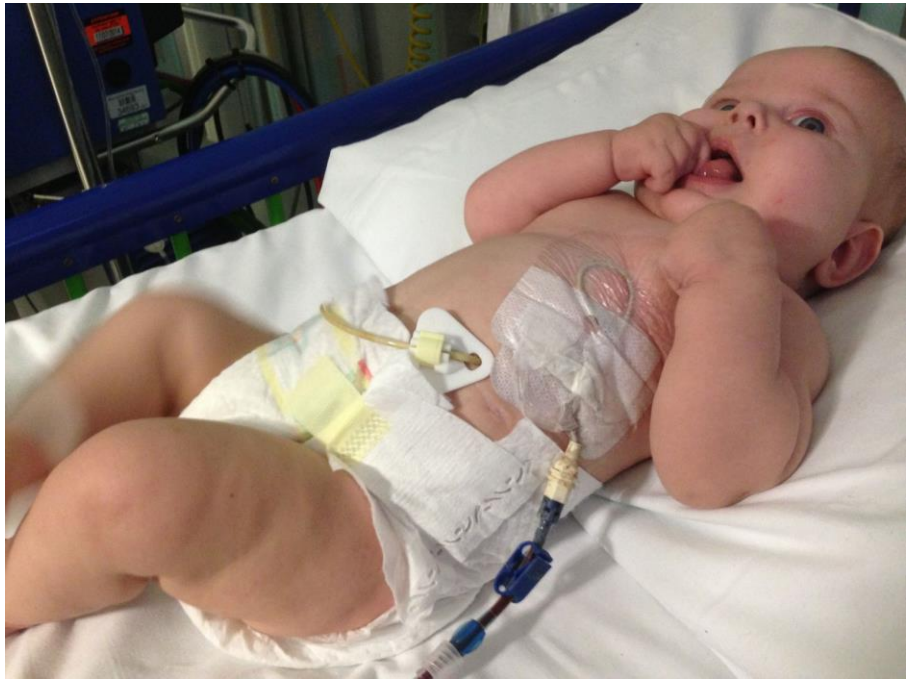
Dialysis in PH

- Unable to reduce oxalate load
- Full week of dialysis oxalate clearance equivalent to 2 days of oxalate production



Am J Kid D 1992; 19: 546-53

Perit Dial Int 1994; 14; 81-84

NDT 2001; 16: 2407-11

KI 2006; 70: 1642-8

Haemodialysis better in PH

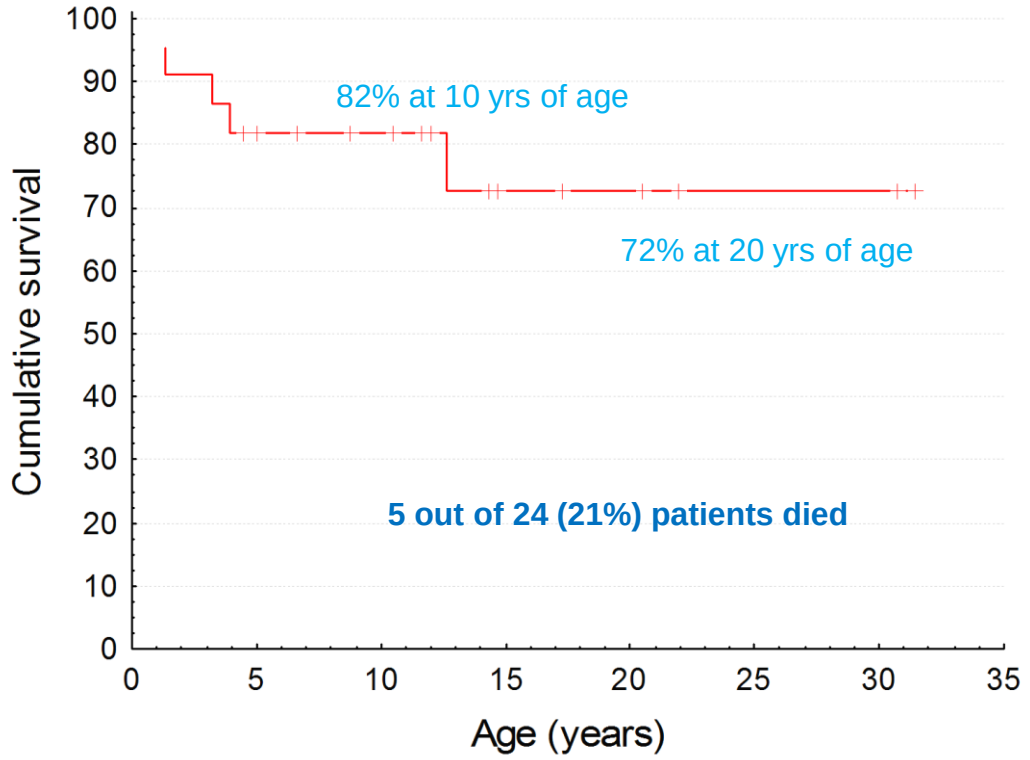
Haemodialysis clearance of oxalate is better than peritoneal but need daily dialysis

Home haemodialysis now favoured option

Isolated liver transplant

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

Patient survival in pre-emptive Liver Tx



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

J Harambat on behalf of
OXALEUROPE

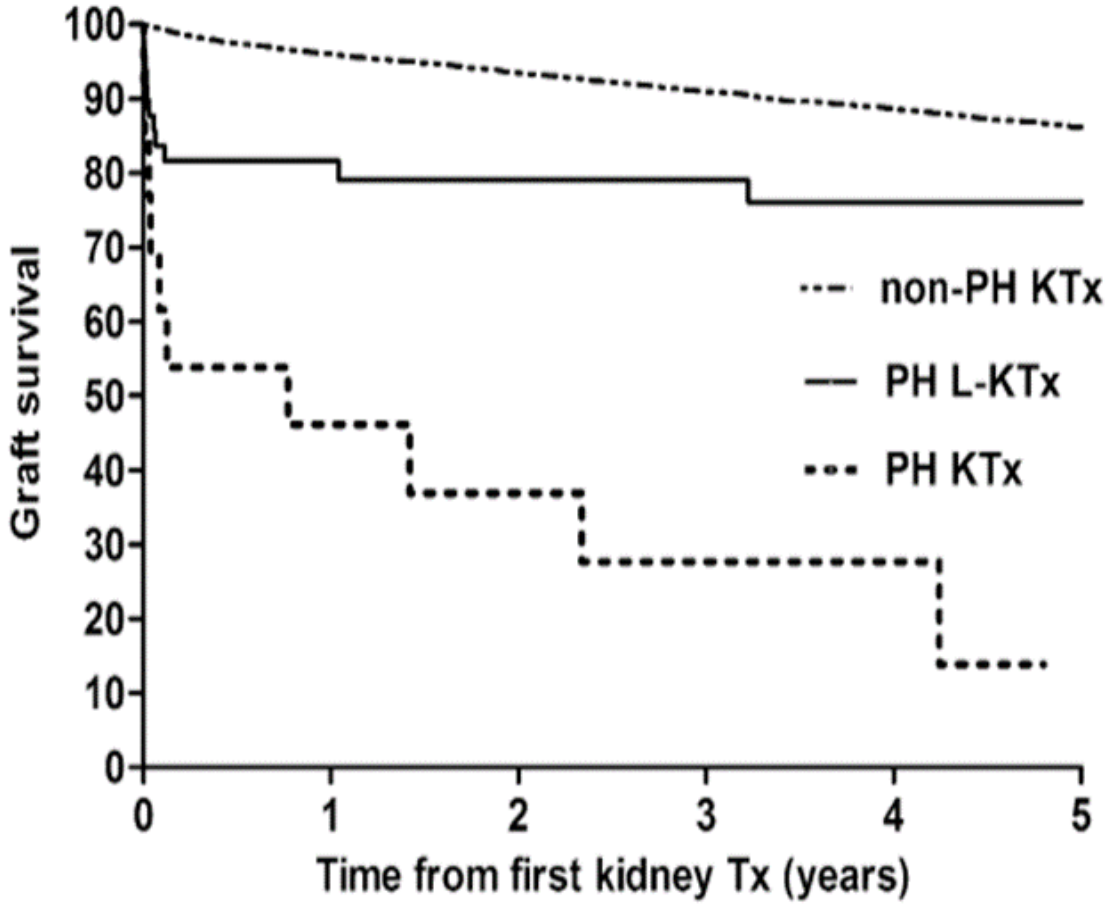
Liver - kidney transplantation: sequential or combined

- Liver 1st then kidney
  - advantage of early liver Tx to stop oxalate production
  - can delay renal Tx
- Deceased donor or LRD or combination
- Liver + kidney Tx at same operation

Ellis et al NDT 2001; 16: 348-54
Heffron TG et al Ped Transpl 2009;13:805-7
Rosenblatt GS et al Urology 2006; 68: 7-8
Malla et al Ped Transpl 2009;13: 782-4
Harambat J et al KI 2010; 77: 383-5
Brinkert F et al Transplant 2009; 15: 1415-21

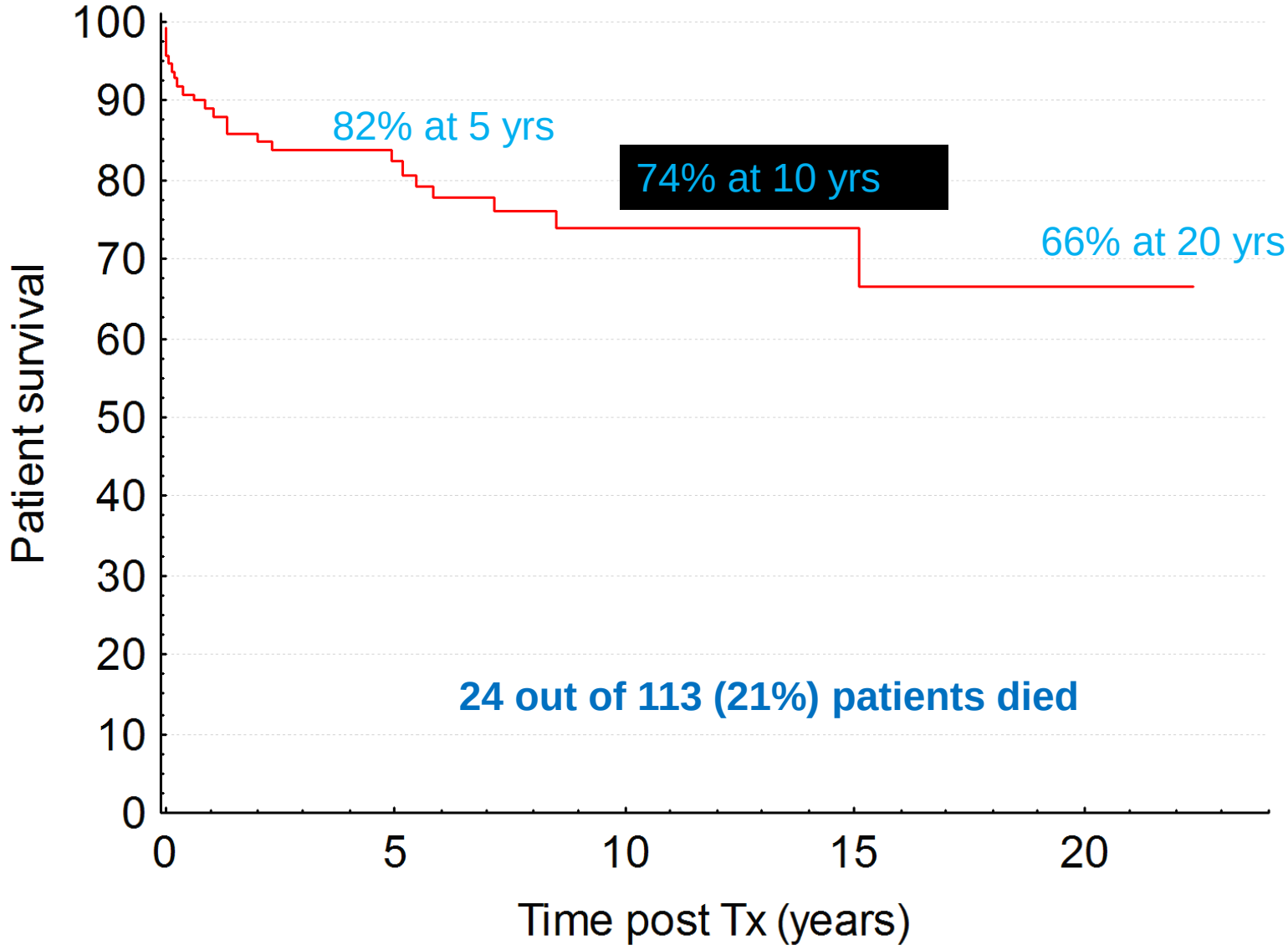
Still need dialysis post liver transplant – maybe years until oxalate clears from bones

Transplantation approach in PH1 5-year kidney graft survival



J et al: Clin J Am Soc Nephrol 2012

Patient survival after combined liver – kidney transplant



J Harambat on behalf of

OXALEUROPE

PH1 long term outcome for liver + kidney transplant

- Success rates with 80% patients surviving 5 yrs but only 74% at 10 yrs
- 20% surgical mortality
- Long term effects post transplant surgery:
  - malignancy PTLD
  - rejection
  - infection
  - Diabetes
- Gradual decline in kidney function

Current problems

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

Lumasiran

Pritesh Gandhi, PharmD.

VP & General Manager, Lumasiran

Alnylam® PHARMACEUTICALS

Claire
Living with primary hyperoxaluria type 1

Primary Hyperoxaluria Type 1

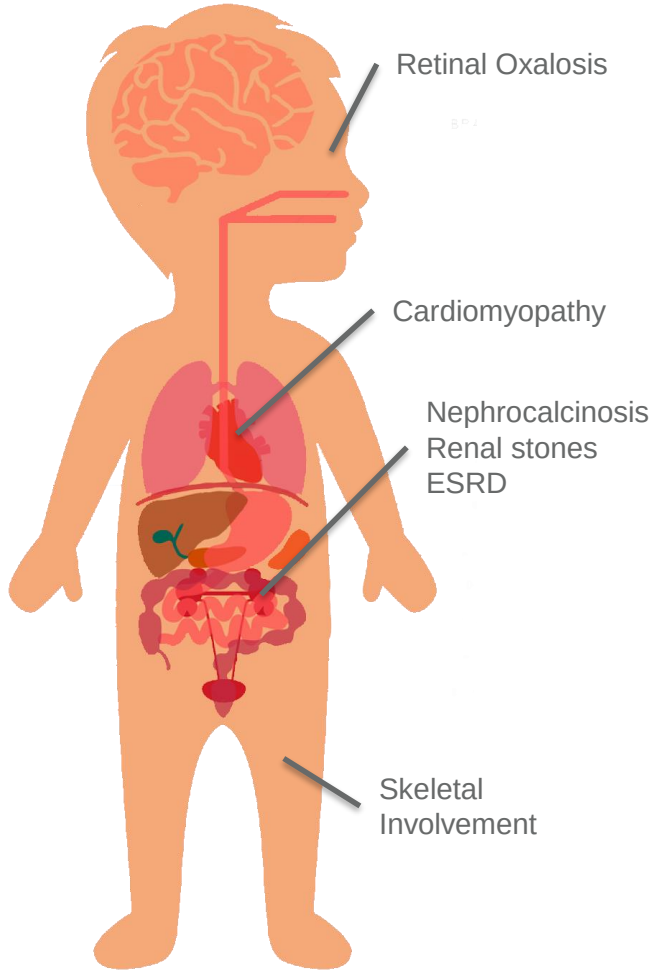
Lumasiran

Description

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

Onset generally
pediatric,
very limited treatment options

Patient Population
~3-5,000
U.S./EU



Alnylam PHARMACEUTICALS

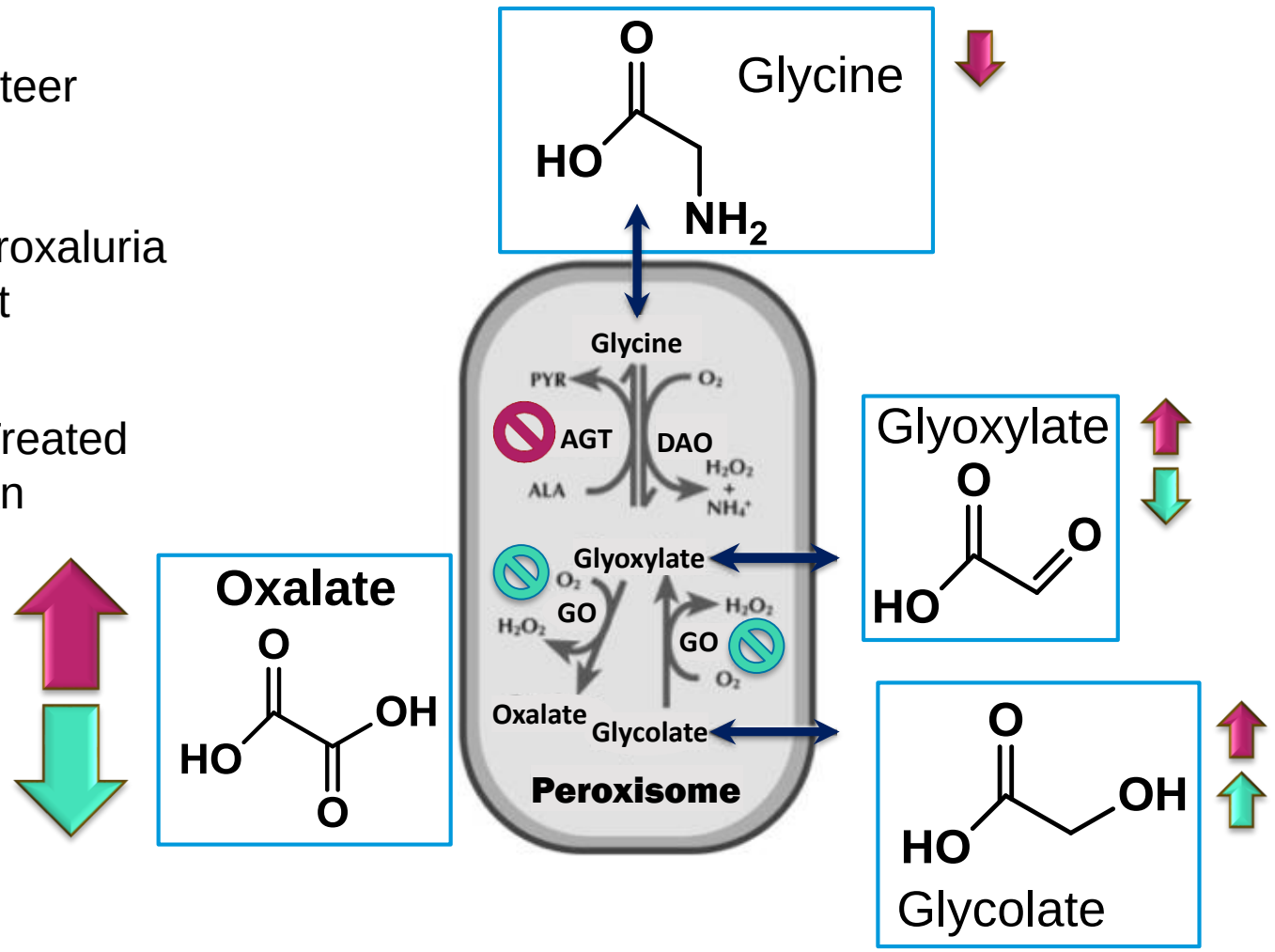
Lumasiran Therapeutic Hypothesis

Knockdown of Liver GO Enzyme to Reduce Oxalate

Healthy Volunteer

Primary Hyperoxaluria Type 1 Patient

PH1 Patient Treated with Lumasiran



Case Report of Healthy Individual with HAO1 Deficiency

Homozygous Loss of Function (LoF) for HAO1 predicted to be *VERY* rare (~1 in every 5 million people)

Healthy volunteer identified by Dr. David van Heel and colleagues of East London Genes and Health through focused genetic study in Bradford, England

- 45-year old healthy female, with predicted homozygous LoF mutations in HAO1
  - History of three successful pregnancies
  - Normal liver function and transaminases, normal renal function and renal ultrasound
  - Urinary glycolate elevated (4x ULN), as well as plasma glycolate, confirming LoF phenotype; UOx and POx normal
- **Rare case report provides further evidence that glycolate oxidase deficiency is well tolerated and that glycolate elevation is not associated with clinical consequences**

Measure	Value	Reference range
Urinary oxalate	0.02 mg/mg CR	<0.048 mg/mg Cr
Plasma oxalate	<1.0 uM/L	<1.6 uM/L
Urinary glycolate	199 mg/g Cr (HIGH)	<50 mg/g Cr
Plasma glycolate	171 nmol/mL (HIGH)	<14 uM nmol/mL

HAO1 = gene encoding for glycolate oxidase (GO) protein

Lumasiran Phase 1/2 Clinical Trial Design

Part A: Healthy adult volunteers (N=32)
Single-Ascending Dose (SAD) | Randomized 6:2, Placebo-controlled

- 0.3 mg/kg x 1 SC, N=8 ✓
- 1.0 mg/kg x 1 SC, N=8 ✓
- 3.0 mg/kg x 1 SC, N=8 ✓
- 6.0 mg/kg x 1 SC, N=8 ✓

✓ Dosing Complete

Part B: Patients with PH1 (N=20)
Multiple-Ascending Dose (MAD) | Randomized 3:1, Placebo-controlled

- 1.0 mg/kg, q28d x 3 SC, N=4 ✓
- 3.0 mg/kg, q28d x 3 SC, N=4 ✓
- 3.0 mg/kg, q84d x 2 SC, N=4 ✓

Expansion Cohorts | Open-label

- 1.0 mg/kg, q28d x 3 SC, N=4 ✓
- 3.0 mg/kg, q28d x 3 SC, N=4 ✓

Part B 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^

- 1.0 mg/kg, q28d SC, N=1
- 3.0 mg/kg, q28d SC, N=2
- 3.0 mg/kg, q84d SC, N=7

- Individual patient dose adjustment may be allowed

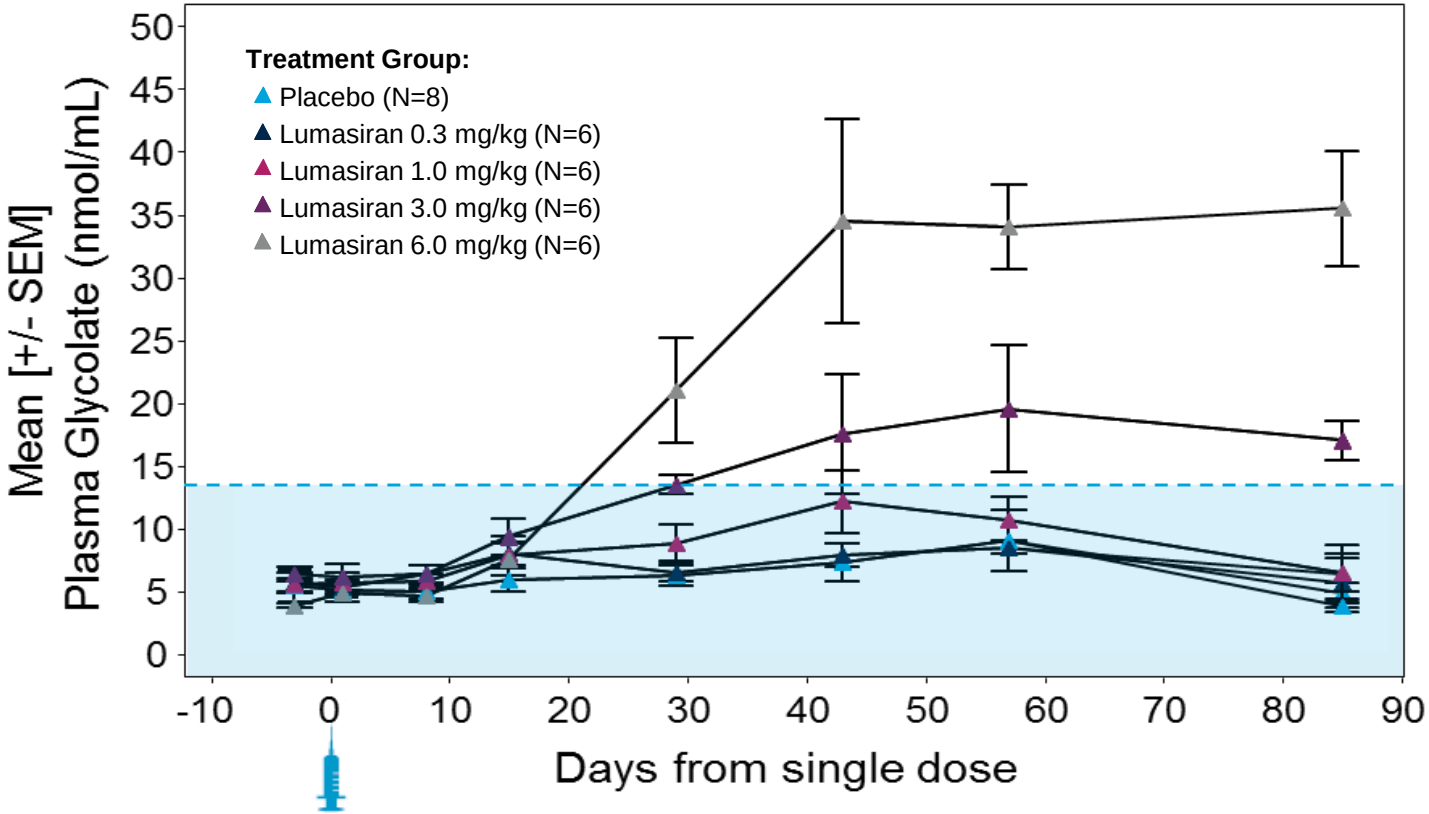
*ClinicalTrials.gov Identifier: NCT02706886; EudraCT Number: 2015-004407-23
^ClinicalTrials.gov Identifier: NCT03350451; EudraCT Number: 2016-003134-24

Alnylam PHARMACEUTICALS

Lumasiran Phase 1/2 Part A Study Results

Plasma Glycolate Levels in Healthy Volunteers

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



Lumasiran Phase 1/2 Study*

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

Baseline Characteristics	Result (N=20)
Mean age, years (range)	14.9 (6–43)
Age <18 years	80%
Gender, females	65%
Mean weight, kg (range)	49.9 (21.3–110.0)
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 Plasma Oxalate Content, µmol/L (range) (N=14†)	8.8 (1.6–19.8)
Mean 24-hour Urine Oxalate:Creatinine Ratio (range)	0.17 (0.07–0.30)
Mean Plasma Glycolate, µmol/L (range)	193.83 (18.0–491.0)

*Data cut-off: 15 Aug 2018
†Not all patients had plasma oxalate assessments due to insufficient sample
PH1, primary hyperoxaluria type 1; eGFR, estimated glomerular filtration rate
Frishberg Y et al. Pediatr Neprol. 2018 (Abstracts – 51st ESPN Meeting, Antalya, Turkey, October 2018)

Lumasiran Phase 1/2 Study*

Disease Characteristics at Study Entry

Characteristic	Result
Time from first symptoms to diagnosis of PH1, mean (years†) (N=13)	1.1 (range: 0.3–5.1)
Time from PH1 diagnosis to first dose of lumasiran, mean (years†) (N=20)	11.3 (range: 2.7–30.8)
Time from first symptoms of PH1 to first dose of lumasiran, mean (years†) (N=13)	13.1 (range: 3.9–34.8)
Results of *AGXT* Genetic Testing, N (%)	20 (100)
Biallelic Missense, N (%)	9 (45)
Biallelic Frameshift, N (%)	5 (25)
Biallelic Nonsense, N (%)	2 (10)
Others, N (%)	4 (20)

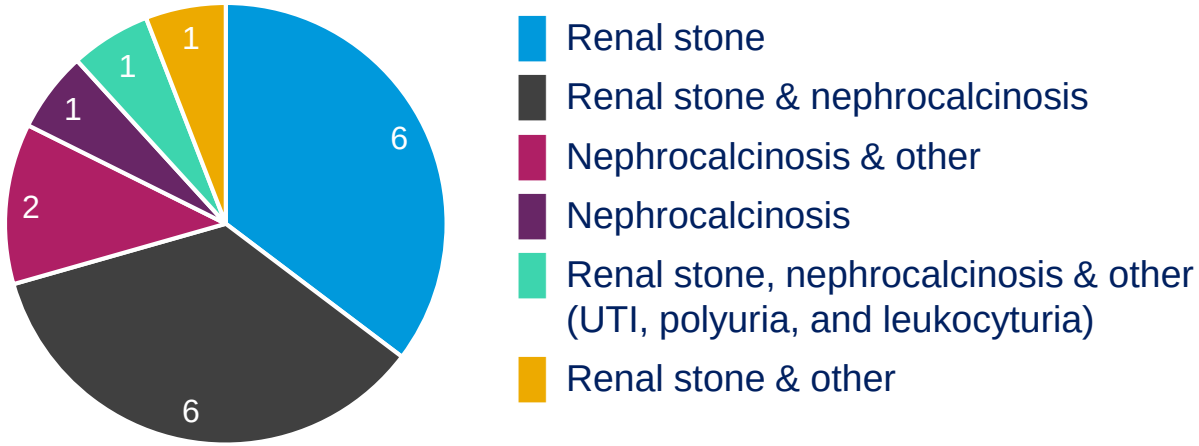
*Data cut-off: 15 Aug 2018
†Any incomplete dates of diagnosis or first symptom where day is unknown but month and year known were imputed to be the first day of the month
PH1, primary hyperoxaluria type 1

Lumasiran Phase 1/2 Study*

Disease Characteristics at Study Entry

Characteristic	Result (N=20)
Patients receiving pyridoxine therapy, N (%)	13 (65)
Mean baseline urinary oxalate content in patients receiving pyridoxine, mmol/24hr/1.73m^2	1.80 (range: 0.83–2.97)
Patient history of symptoms at study entry, N (%)	
Renal stones	18 (90)
Nephrocalcinosis	13 (65)
Urinary Tract Infection	9 (45)
Pyelonephritis	8 (40)

Patients with ≥1 symptom present at diagnosis, by symptoms (N=17)



Lumasiran Phase 1/2 Study Initial Results*

Safety: Part B (Patients with PH1)

Multiple doses of lumasiran well tolerated in patients with PH1

- No discontinuations from study treatment
- SAEs reported in 1 (33%) placebo-treated patient and 5 (25%) lumasiran-treated patients; none related to study drug
  - Placebo: 1 patient with SAE of acute pyelonephritis and kidney stones
  - Lumasiran: 2 patients with kidney stones; 1 patient with vomiting; 1 patient with gastroenteritis; and 1 patient with abdominal pain, fever and vomiting
- AEs reported in 3 (100%) placebo-treated patients and 19 (95%) lumasiran-treated patients
  - Majority of AEs were mild or moderate in severity and unrelated to study drug
  - Severe AEs reported in 1 (33%) placebo-treated patient (acute pyelonephritis) and 2 (10%) lumasiran-treated patients (1 patient with acute renal colic and kidney stone, and 1 patient with kidney stone); none related to study drug
  - AEs reported in >3 patients receiving lumasiran: vomiting, pyrexia, cough (n=6 each); abdominal pain, headache (n=5 each); and rhinitis (n=4)
  - Self-limiting injection site reactions (ISRs) reported in 3 (15%) patients receiving lumasiran; all mild or moderate
- No clinically significant laboratory changes

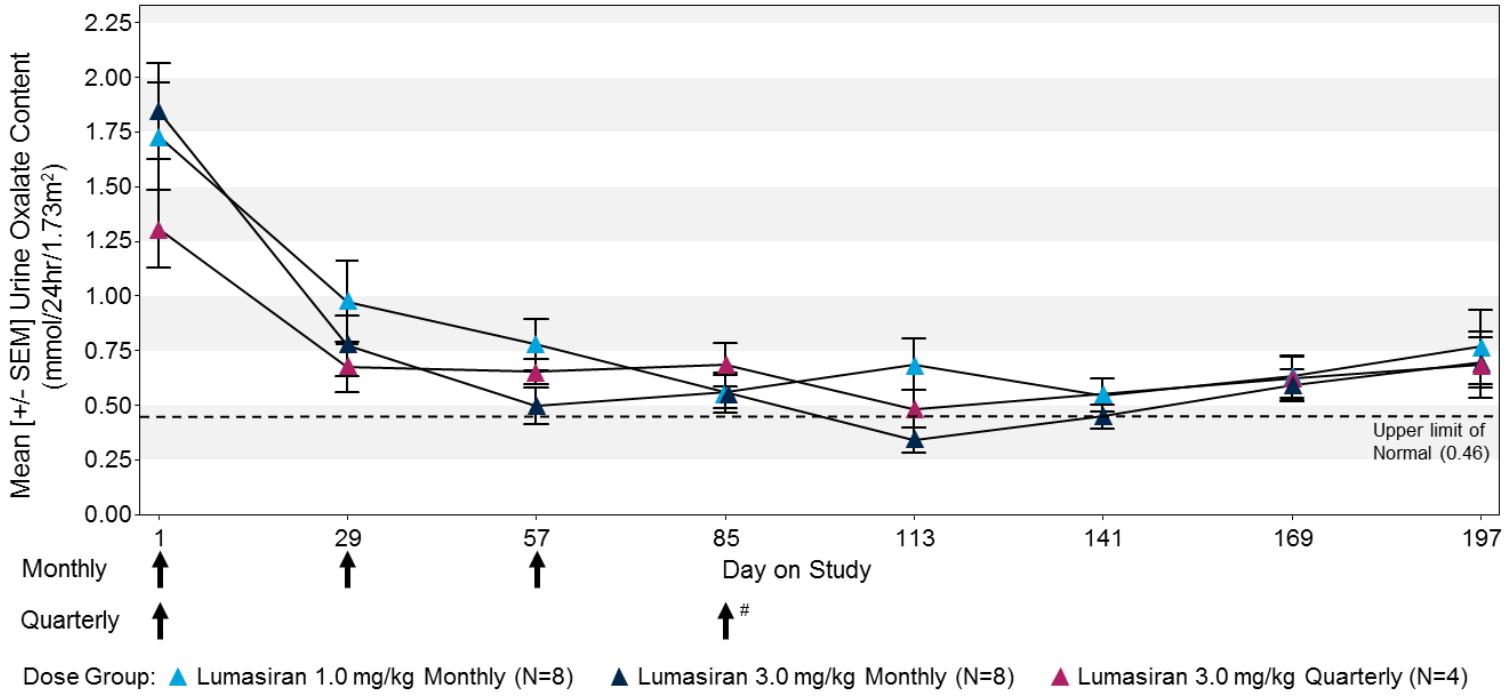
*Data cut-off: 15 Aug 2018
PH1, primary hyperoxaluria type 1; SAE, serious adverse event; AE, adverse event

Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Urinary Oxalate Content in Part B (Patients with PH1)

Lumasiran treatment led to 75% mean maximal reduction in urinary oxalate (range: 43-87%) relative to baseline† (n=20)

- 66% mean reduction relative to baseline 28 days post last dose of lumasiran



*Data cut-off: 15 Aug 2018 ; Only data points with at least 3 contributing patients are represented.
†Patients who completed the Study Day 85 visit and had a valid 24-hour urinary oxalate assessment; placebo data not shown due to limited valid collections
#Patients randomized to placebo received subsequent dosing of lumasiran and are included in the lumasiran dosing cohort in which they were randomized with day 1 relative to first dose of lumasiran; patient randomized to placebo in 3 mg/kg quarterly dosing only received a single dose of lumasiran on Day 1
PH1, primary hyperoxaluria type 1
Frishberg Y et al. Pediatr Neprol. 2018 (Abstracts – 51st ESPN Meeting, Antalya, Turkey, October 2018)

Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Urinary Oxalate Reduction in Part B (Patients with PH1)

Urinary Oxalate Reduction	Result
Mean reduction 28 days post last dose of lumasiran (N=20)	66%
1.0 mg/kg monthly (N=8)	66%
3.0 mg/kg monthly (N=8)	68%
3.0 mg/kg quarterly (N=4)	63%
Patients achieving <0.46 [upper limit of normal]	13/20 (65%)
1.0 mg/kg monthly	3/8 (38%)
3.0 mg/kg monthly	6/8 (75%)
3.0 mg/kg quarterly	4/4 (100%)
Patients achieving <0.69 [1.5x upper limit of normal]	20/20 (100%)

Among patients receiving 3.0 mg/kg monthly or quarterly doses of lumasiran, 10/12 (83%) achieved urinary oxalate levels within the normal range

*Data cut-off: 15 Aug 2018
PH1, primary hyperoxaluria type 1
Frishberg Y et al. Pediatr Neprol. 2018 (Abstracts – 51st ESPN Meeting, Antalya, Turkey, October 2018)

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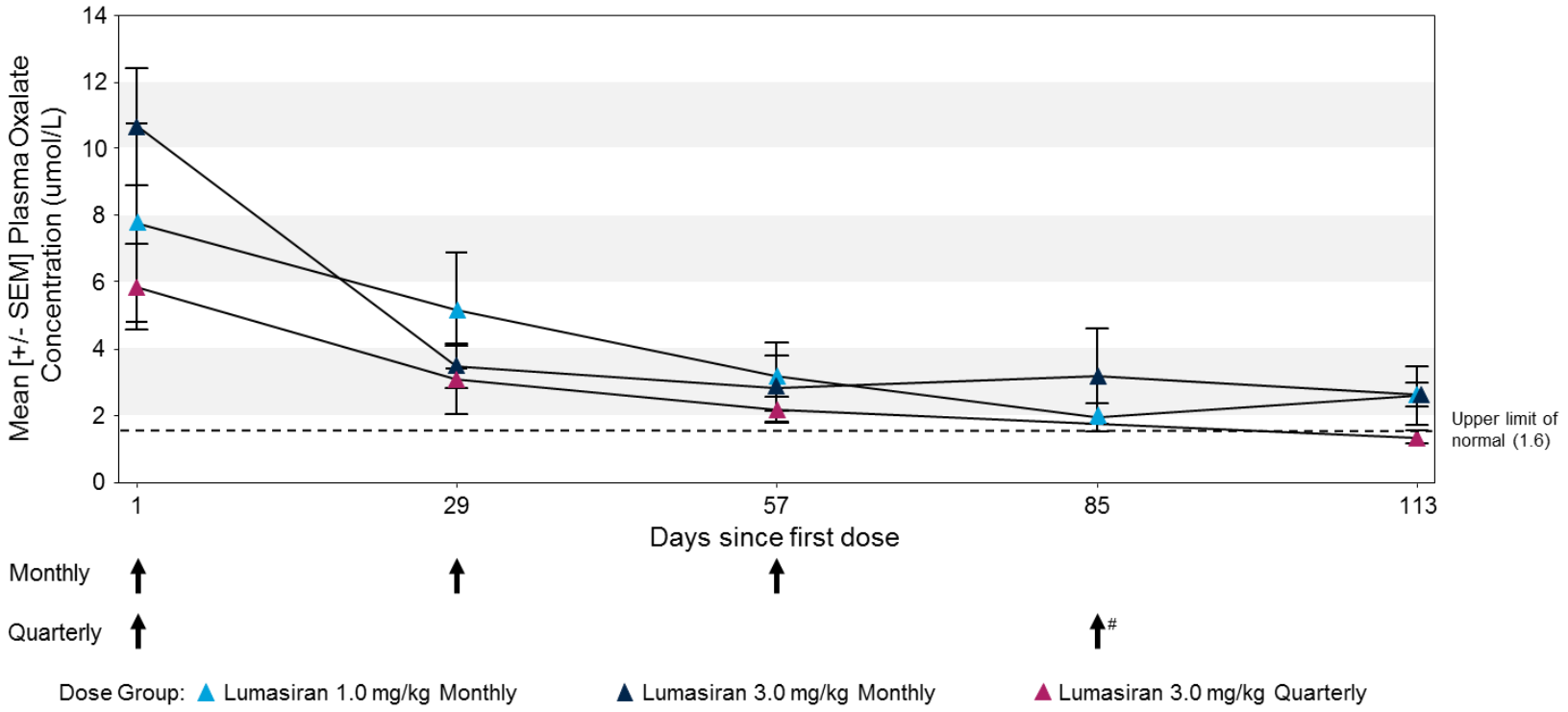
Lumasiran Phase 1/2 Study Initial Results*

Pharmacodynamics: Plasma Oxalate Content in Part B (Patients with PH1)

Lumasiran treatment led to 75% mean maximal reduction in plasma oxalate (range: 57-94%) relative to baseline (N=10†)

- 59% mean reduction relative to baseline 28 days post last dose of lumasiran
- 50% of patients achieved plasma oxalate levels within the normal range (<1.6 µmol/L)



*Data cut-off: 15 Aug 2018; Only data points with at least 3 contributing patients are represented.
†Not all patients had plasma oxalate assessments due to insufficient sample; results reported as <1 µmol/L assigned value of 1
#Patients randomized to placebo received subsequent dosing of lumasiran and are included in the lumasiran dosing cohort in which they were randomized with day 1 relative to first dose of lumasiran; patient randomized to placebo in 3 mg/kg quarterly dosing only received a single dose of lumasiran on Day 1
PH1, primary hyperoxaluria type 1

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Lumasiran Phase 2 OLE Study Initial Results*

Safety

Continued dosing with lumasiran was well tolerated in patients with PH1

- No discontinuations from study treatment
- SAEs reported in 2/8 patients (25%); none assessed as related to study drug
  - 1 patient with traumatic brain injury and contusion; 1 patient with nephrolithiasis†
- AEs reported in 5/8 (63%) of patients
  - AEs were mild or moderate in severity and majority were assessed as unrelated to study drug
- No injection site reactions reported
- No clinically significant laboratory changes

*Data cut-off: 3 Oct 2018
†SAE of nephrolithiasis occurred prior to patient receiving first dose in OLE study
OLE, open-label extension; PH1, primary hyperoxaluria type 1; SAE, serious adverse event; AE, adverse event

ILLUMINATE-A*: Lumasiran Phase 3 Study

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

Patient Population
N = 30

- Adults & children ≥6 years
- Urinary oxalate excretion ≥0.7 mmol/24hr/1.73m^2
- Confirmed alanine glyoxalate aminotransferase (*AGXT*) mutations
- eGFR >45 mL/min/1.73m^2

2:1 Randomization

6-Month Double Blind Treatment Period

Lumasiran
Three monthly loading doses then maintenance dose of 3.0 mg/kg†

Placebo
Equivalent volume for 3 monthly loading doses then maintenance

54-Month Extension Period

Lumasiran
3.0 mg/kg every 3 months
(following loading doses for patients previously receiving placebo)

Primary Analysis at 6 Months

Primary Endpoint
- Percent change in 24-hour urinary oxalate excretion

Secondary Endpoints
- Change in 24-hour urinary oxalate:creatinine ratio
- Proportion of patients with 24-hour urinary oxalate level below ULN and 1.5x ULN
- Change in eGFR

Topline results expected in late 2019

NDA submission planned in early 2020
(assuming positive results)

FDA Breakthrough and EMA PRIME Designations

*NCT03681184; EudraCT Number: 2018-001981-40
Month, 28 days
† 3.0 mg/kg once monthly for 3 consecutive months (loading dose phase) followed by 3.0 mg/kg once every 3 months (maintenance phase) starting 1 month after last loading dose

Lumasiran Registrational Program

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

ILLUMINATE-A

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

ILLUMINATE-B

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

ILLUMINATE-C

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

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Lumasiran Market Opportunity

Lumasiran has potential to address significant unmet needs

- Current treatment options are limited
- Most patients have symptoms by age 25

Significant economic burden

- Average cost can exceed $1 million (transplant and life-long immunosuppression)

Disease significantly under-diagnosed

- Approx. 40-50% of patients remain undiagnosed
- In adults, mean time from initial symptoms to diagnosis was 6.2±10.5 years
- In adult patients, 30-65% of patients do not get diagnosed until end-stage renal disease

Education efforts increase disease awareness and accelerate time to diagnosis

- Primary focus on nephrologists and urologists
- Partnerships with patient advocacy group

Initial opportunity in Primary Hyperoxaluria Type 1

Potential for further expansion

Systemic Oxalosis in PH1

Idiopathic stone formation refractory to standard of care

AlnylamAct™

Program Launch (2018)

1. Primary Hyperoxalurias
Three-gene testing for Primary Hyperoxalurias (*AGXT*, *GPHPR*, *HOGA1*)

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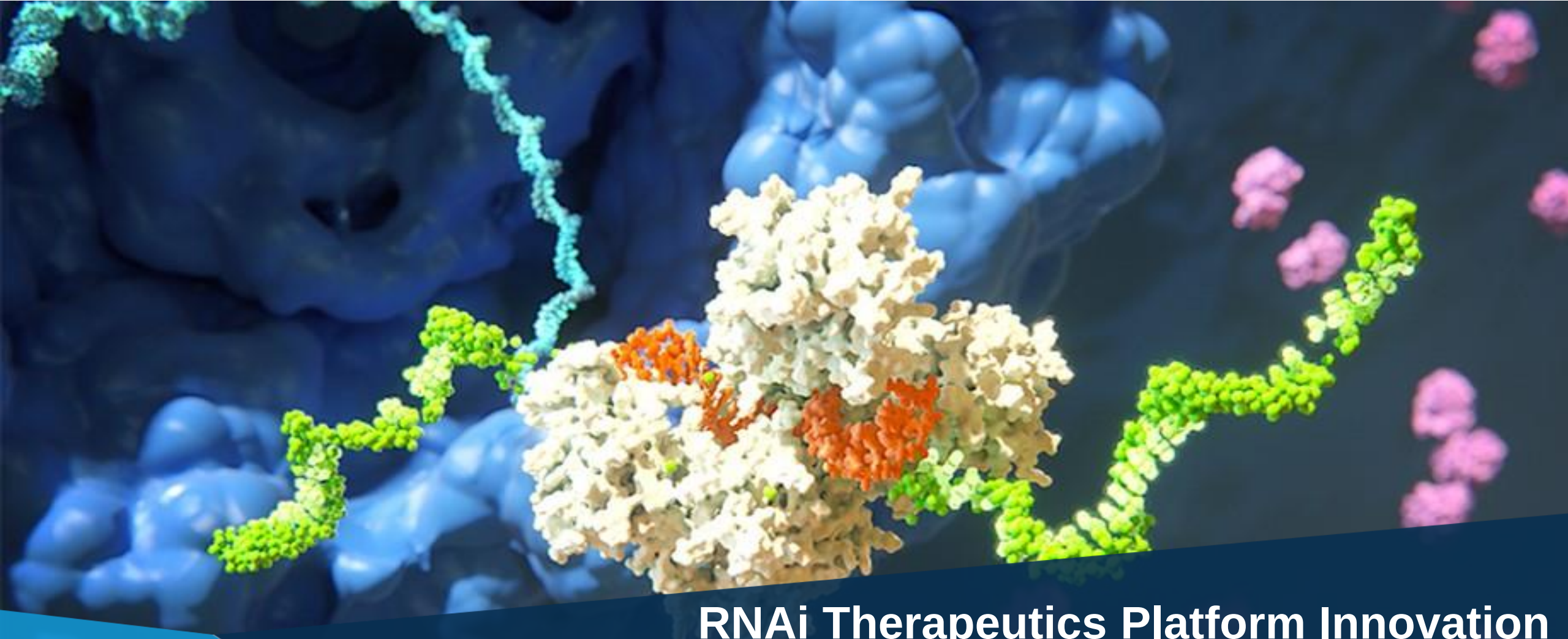

RNAi Therapeutics Platform Innovation

Kevin Fitzgerald, Ph.D.

SVP, Research

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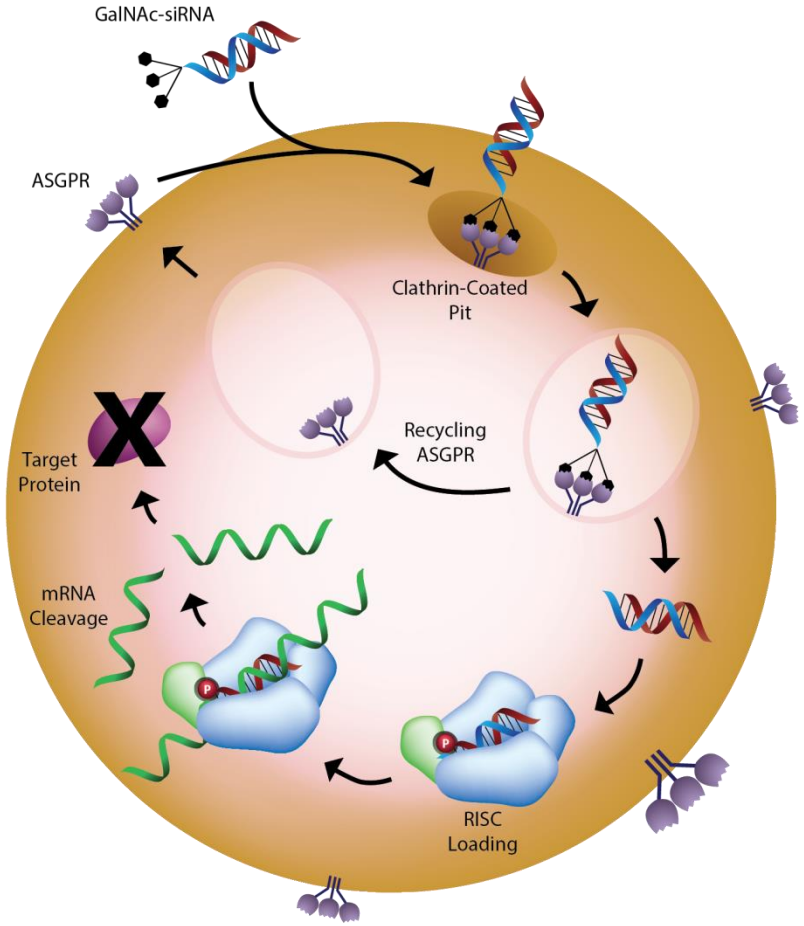
SubQ Conjugate Platform for Targeted Delivery to Liver

siRNA

- Metabolic stability
- Intrinsic potency
- Specificity

Asialoglycoprotein Receptor (ASGPR)

- Highly expressed in hepatocytes
- High capacity receptor
- Conserved across species



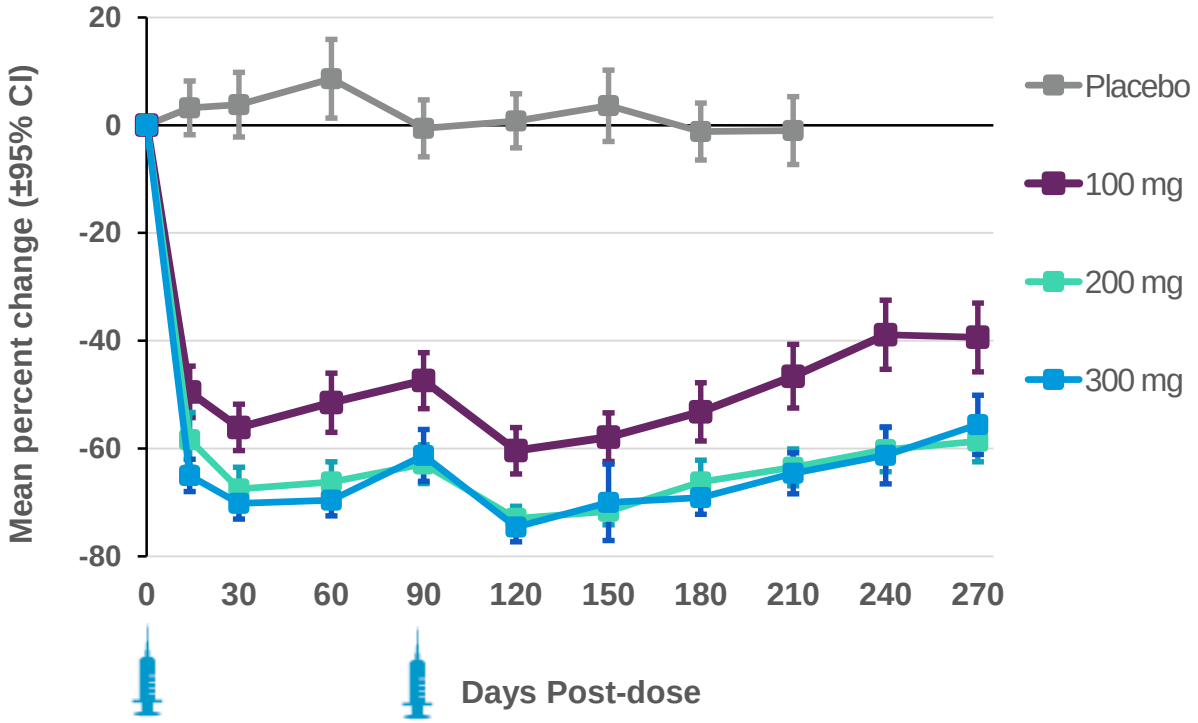
Ligand

- Trivalent GalNAc
- High affinity and specificity

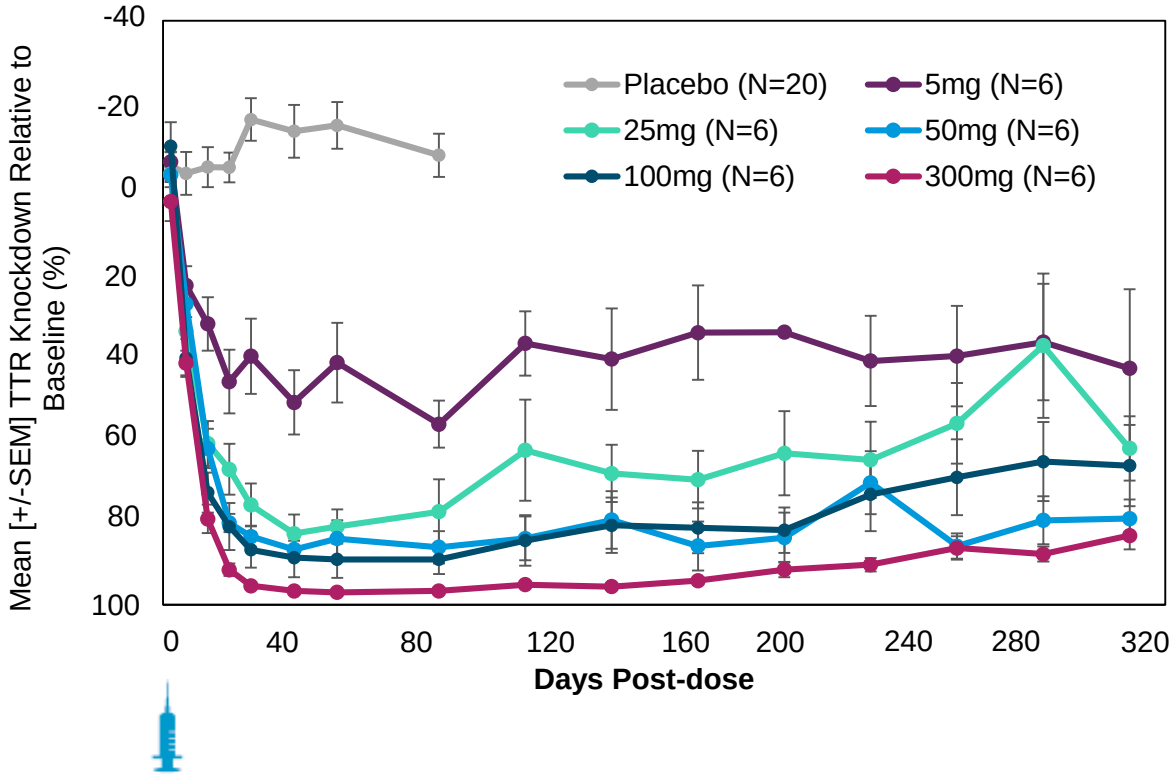
Nair et al. *JACS* 2014
Matsuda et al. *ACS Chem. Bio.* 2015
Rajeev et al. *ChemBioChem* 2015
Nair et al. *NAR* 2017
Foster et al. *Mol. Ther.* 2018
Janas et al. Nat. com. 2018

Highly Reproducible Platform for Target Gene Knockdown

Inclisiran (PCSK9)



Vutrisiran (TTR)*



Ray et al., *N Engl J Med.* 2017 Apr 13;376(15):1430-1440

*As of data cut-off on 31May2017

RNAi Therapeutics: Extensive Human Safety Experience

Encouraging Profile to Date

Number of Programs	Number of Clinical Studies	Total Patients or Volunteers Dosed	Greatest Duration of Exposure
>15	>36	>3500	>60 months

Minimal platform related findings*

- Low incidence (~3%) of generally mild, asymptomatic, reversible LFT increases >3x ULN
- Injection site reactions (~20%) generally mild, transient and rarely led to discontinuation
  - No events of ulceration, necrosis or tissue damage
- One report of anaphylaxis (<0.05%) in patient with prior history of atopy**
- No evidence of broader platform implications from revusiran program discontinuation in 2016
  - Revusiran employed earlier generation STC platform and 12-280x higher doses

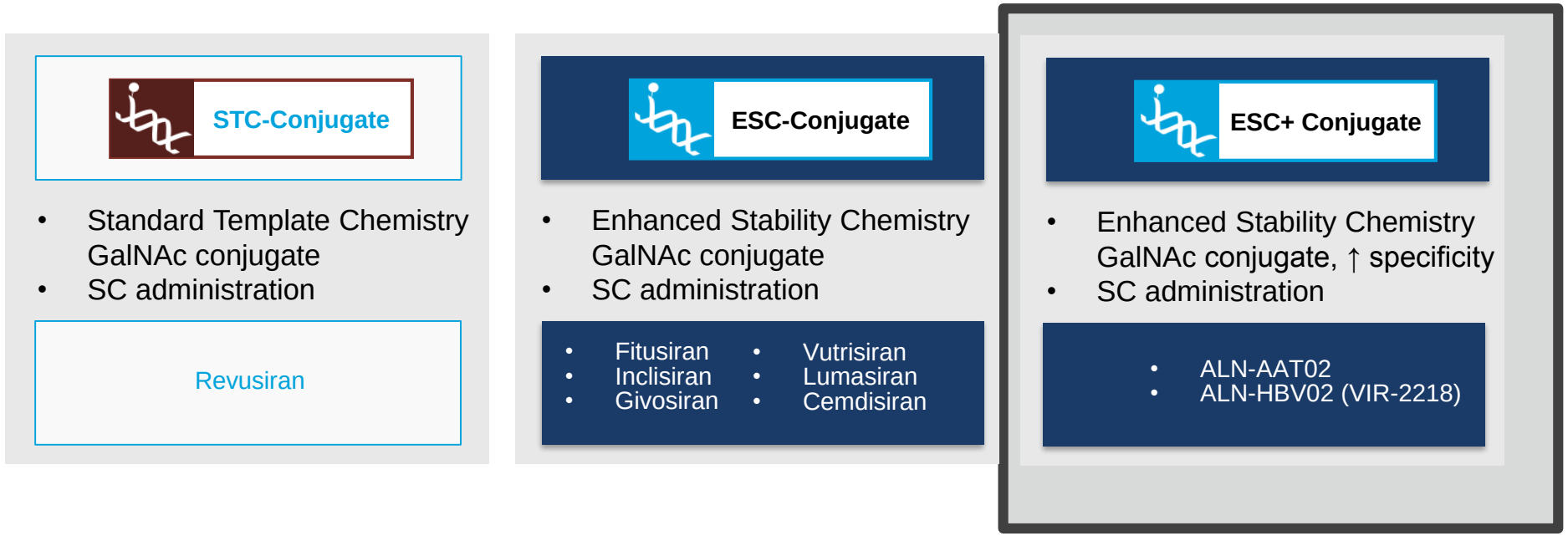
Favorable emerging profile for ESC-GalNAc platform compared with competing oligo platforms†

- No evidence of thrombocytopenia, renal toxicity, or systemic inflammatory effects

*Experience as of October 2018 – Data estimated based on available safety data
**Givosiran OLE study, reported April 2018
† Not based on direct comparative studies

Alnylam PHARMACEUTICALS

Next Generation of Conjugates: ESC+



First generation GalNAc conjugate, initial human POC

Second generation GalNAc conjugate, human POC, greater potency and durability with lower exposures

Next generation GalNAc conjugate with further improvements to specificity and therapeutic index

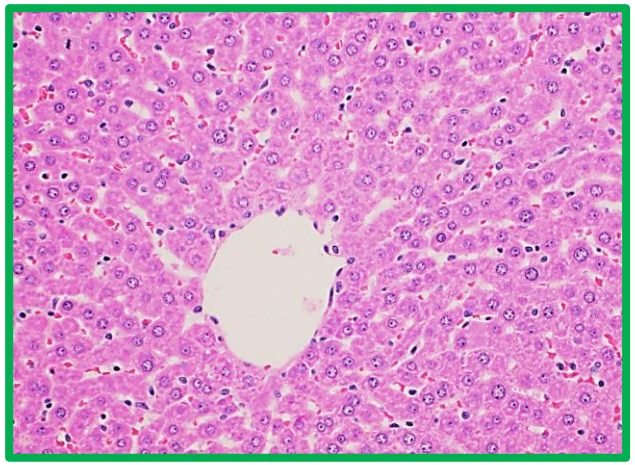
Janas et al. *Nat Commun*. 2018 Feb 19;9(1):723

Subset of ESC Conjugates in Rodents: LFTs at Exaggerated Doses

In silico prediction & *In vitro* efficacy → *In vitro* screen for predicted off-targets → Rodent Knockdown → **Rat Tox @ >100x PD dose** → NHP Knockdown → DC

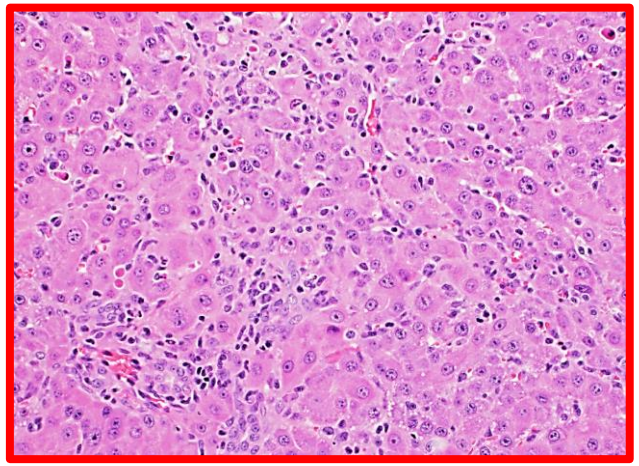
Good Actors

No LFTs



Bad Actors

↑LFT 2x upper limit of normal



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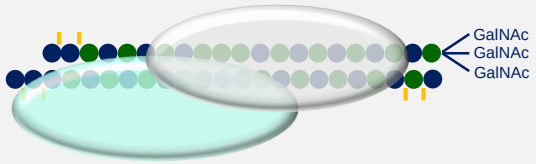
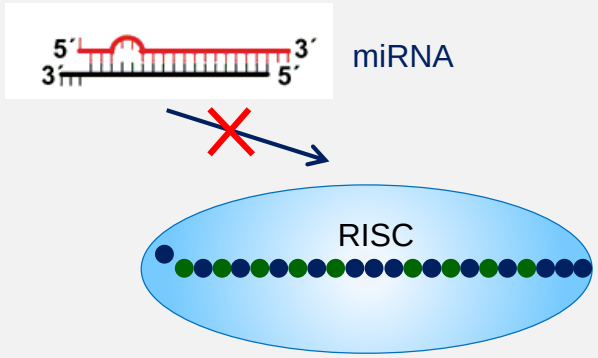
Seed-Based Off-Target Effects Are Important Drivers of Rodent Hepatotoxicity for Subset of Conjugates

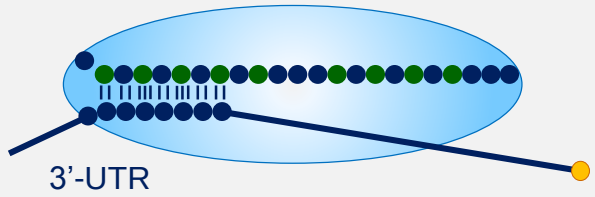
1. Non-RNAi effects
   e.g. siRNA chemistry, metabolites protein binding, drug accumulation



2. Competition for RISC loading with miRNAs



3. Undesired seed-based off-target activity



Off-target binding
Partial sequence match

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-02989-4 OPEN

Selection of GalNAc-conjugated siRNAs with limited off-target-driven rat hepatotoxicity

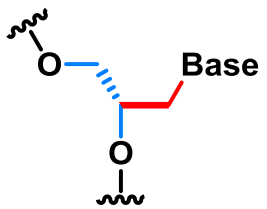
Maja M. Janas[1], Mark K. Schlegel[1], Carole E. Harbison[1], Vedat O. Yilmaz[1], Yongfeng Jiang[1], Rubina Parmar[1], Ivan Zlatev[1], Adam Castoreno[1], Huilei Xu[1], Svetlana Shulga-Morskaya[1], Kallanthottathil G. Rajeev[1], Muthiah Manoharan[1], Natalie D. Keirstead[1], Martin A. Maier[1] & Vasant Jadhav[1]

Janas et al. *Nat Commun*. 2018 Feb 19;9(1):723

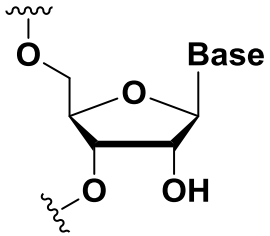
Alnylam PHARMACEUTICALS

GNA: One Potential Solution

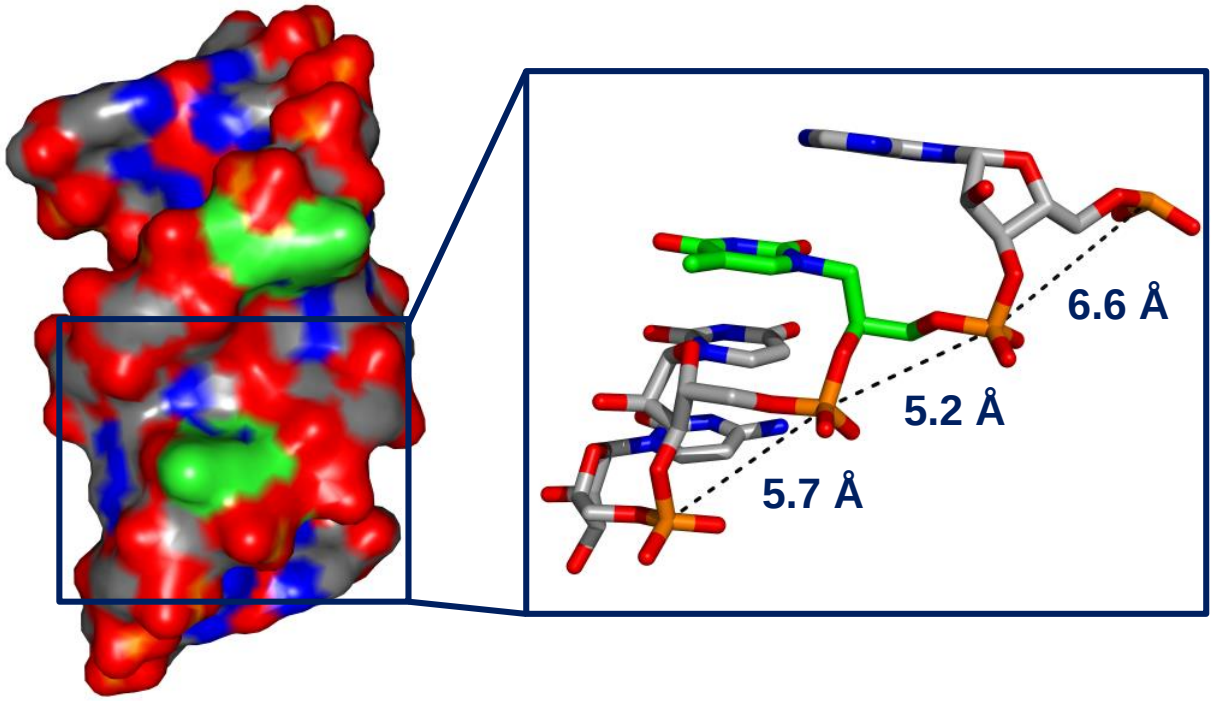
- Glycol Nucleic Acid (GNA) in seed region generally appears to be well-suited to minimize off-target effects via **seed-pairing destabilization** while maintaining potency
- GNA can be well accommodated within the RNA duplex despite shorter phosphate-phosphate and base-backbone distance



(*S*)-GNA



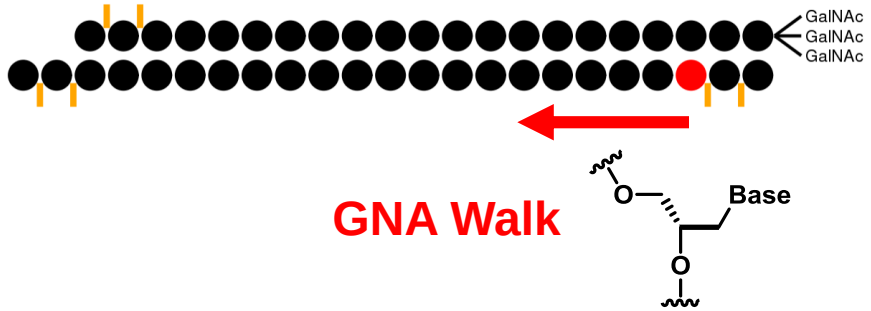
RNA



Schlegel et al. *J. Am. Chem. Soc.* 2017, 139, 8537.

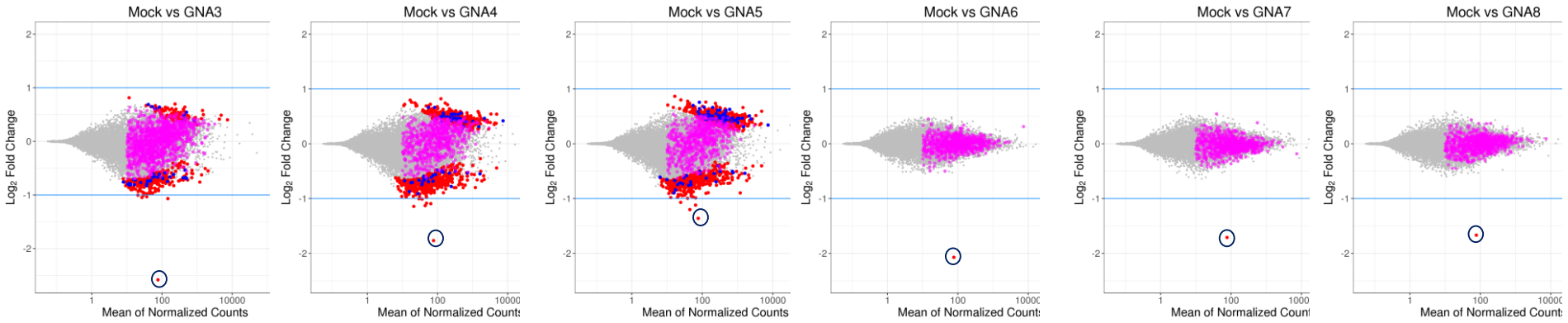
GNA at 6-8 Demonstrates Superior Off-Target Mitigation vs. 3-5

In Vitro RNAseq: High Dose



DEGs (Differentially Expressed Genes)
3'UTR match, significant
3'UTR match, not significant

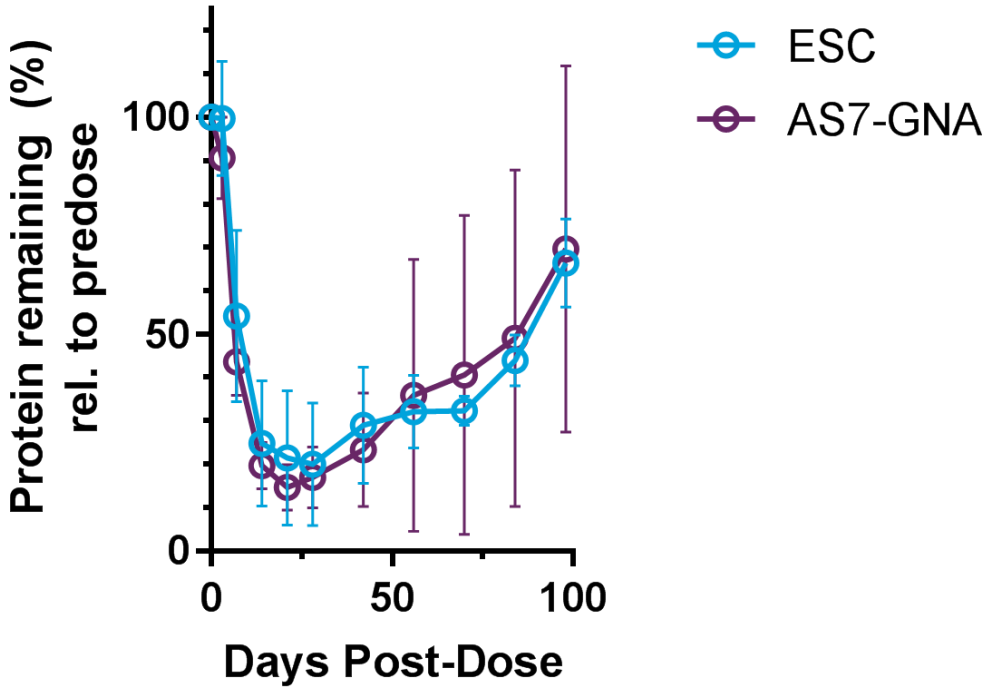
GNA Series



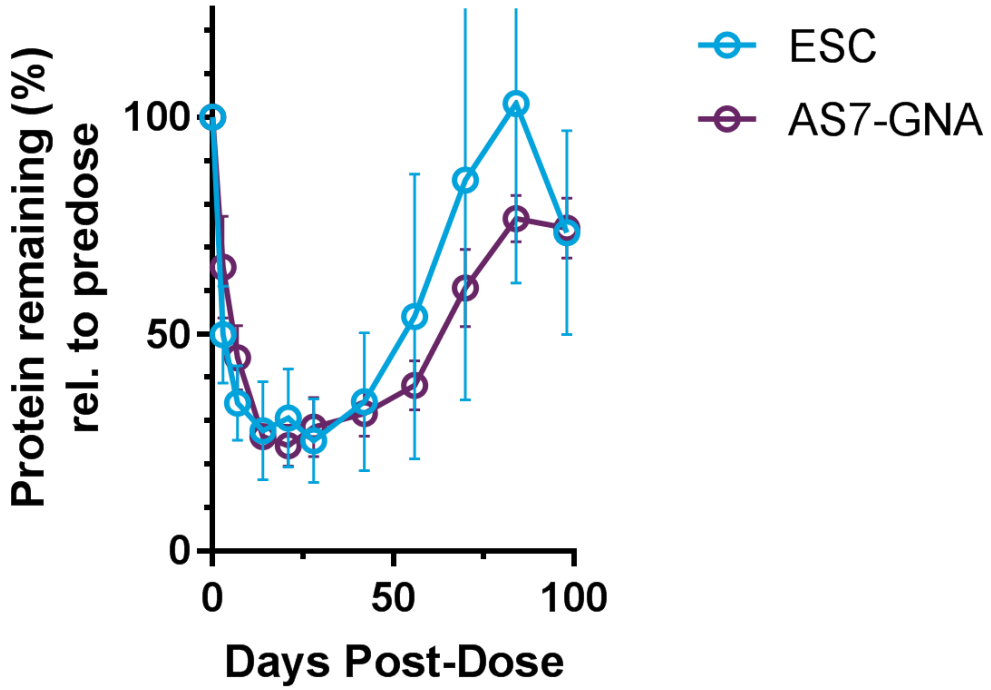
"Clean" Desired Profiles

ESC+ Conjugates (GNA) Are as Efficacious as ESC in NHP

Example 1



Example 2



ESC+ Summary

- **RNAi-mediated off-target effects are important drivers of LFTs in rodent toxicity studies**

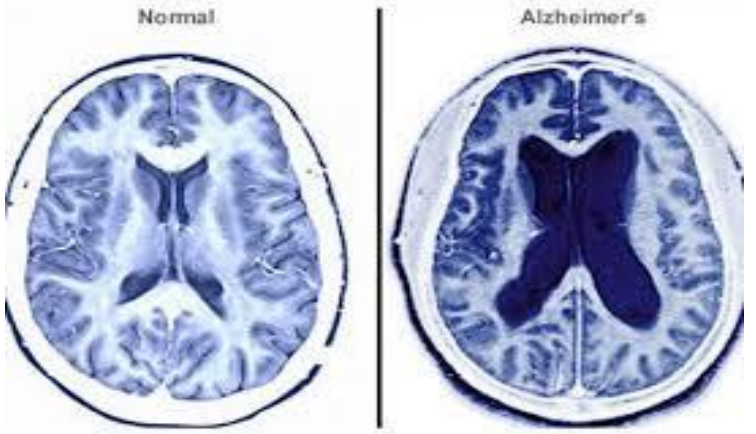
- **Developed ESC+ strategy to mitigate seed-mediated off-target effects**
  - Glycol nucleic acid (GNA), in seed region of antisense strand
  - Pharmacodynamics of ESC+ design translates across species
  - Improves specificity and expands therapeutic index

- **Multiple ESC+ conjugates are advancing towards or in clinical development**
  - ALN-HBV02 (VIR-2218): FIM dosed
  - ALN-AAT02: CTA filed and approved
  - ALN-AGT: expected 2019 filing

RNAi Therapeutics for CNS Diseases

No Current Therapies to Prevent or Reverse Neurodegenerative Disease

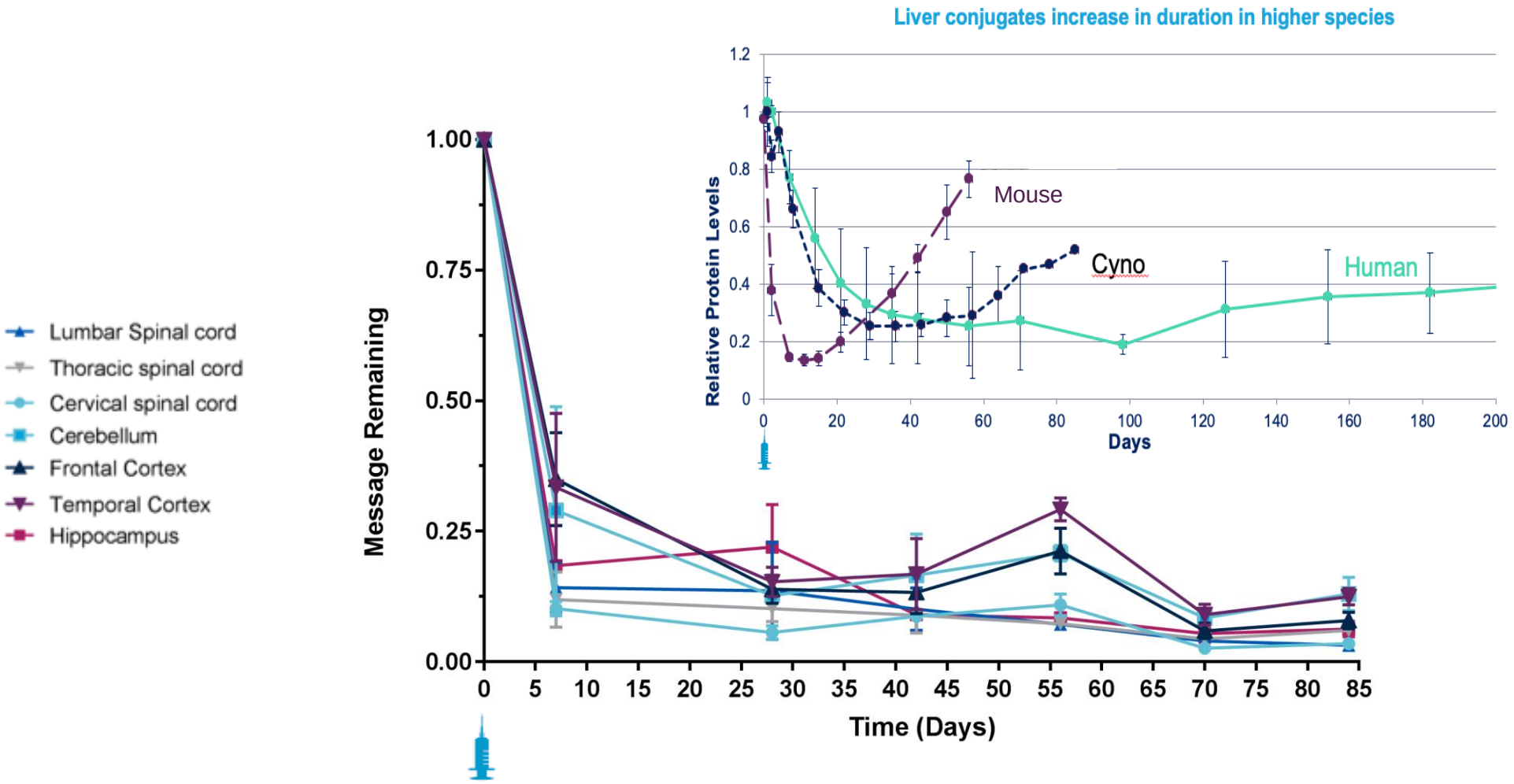
- Dominantly inherited neurodegenerative diseases include
  - Alzheimer's disease
  - Amyotrophic lateral sclerosis (ALS)
  - Frontotemporal dementia
  - Huntington's disease
  - Parkinson's disease
  - Prion disease
  - Spinocerebellar ataxia
  - Many other orphan genetic diseases with CNS component



- Number of genetically validated targets known but no current disease modifying therapies for these devastating, life threatening disorders
- RNAi therapeutics directed to disease-causing, CNS-expressed genes represent next great frontier
- Expect superior potency, duration and systemic safety profile vs. ASOs

Alnylam PHARMACEUTICALS

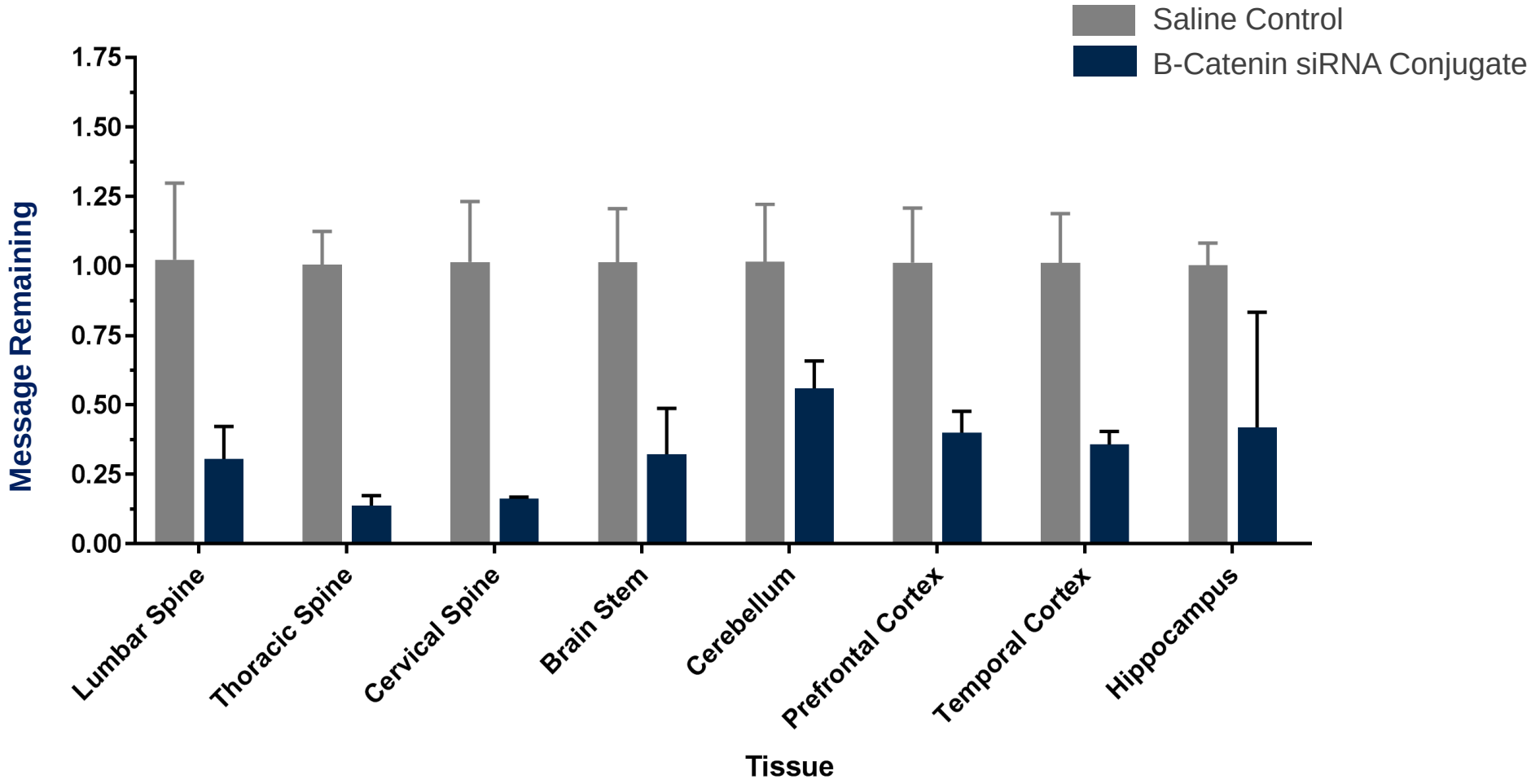
SOD1 mRNA Knockdown in Rat CNS Following Single IT Bolus



- >90% reductions across CNS
- Expect bi-annual or potentially less frequent dose regimens

Robust Silencing Across CNS Demonstrated in NHP

Target Knockdown at Day 31

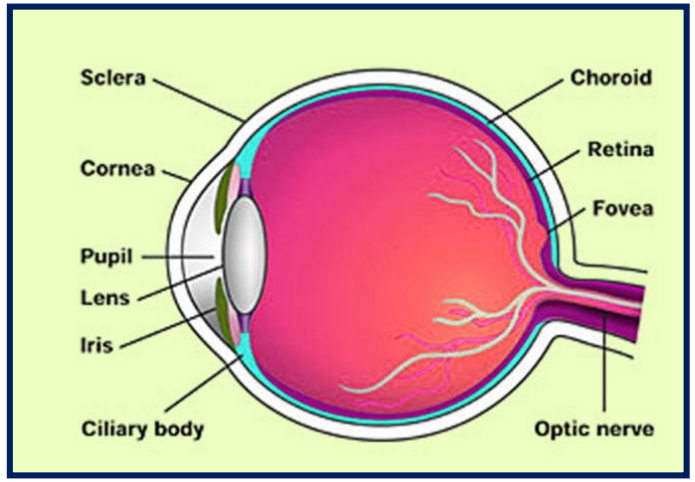


Conjugate robust knockdown throughout the CNS Day 31 post a single dose

RNAi Therapeutics for Ocular Diseases

Disease-Causing, Intraocular Gene Targets Represent Significant Opportunity

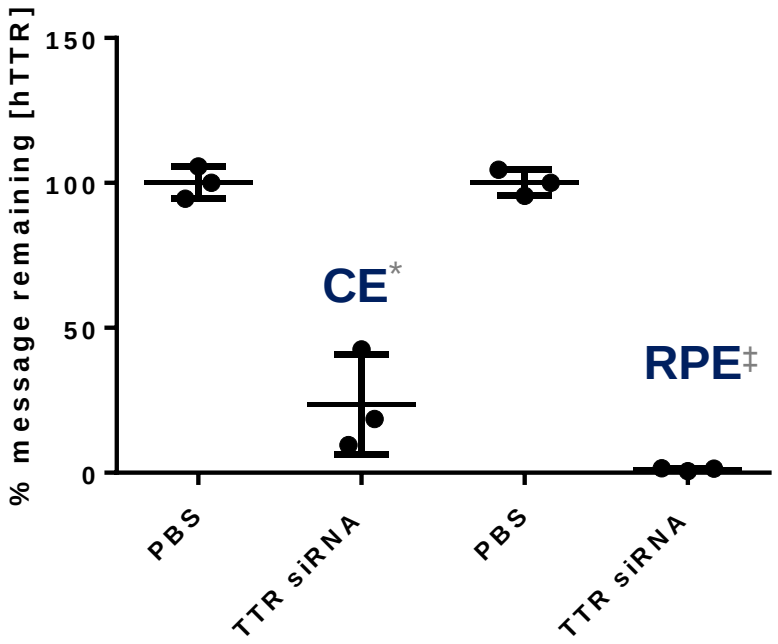
- Examples of ocular diseases well suited for RNAi therapies
  - AMD, Dry
  - AMD, Wet
  - Dominant Retinitis Pigmentosa 4
  - Glaucoma
  - hATTR
  - Hereditary juvenile open angle glaucoma
  - SCA7
  - Stargardt disease



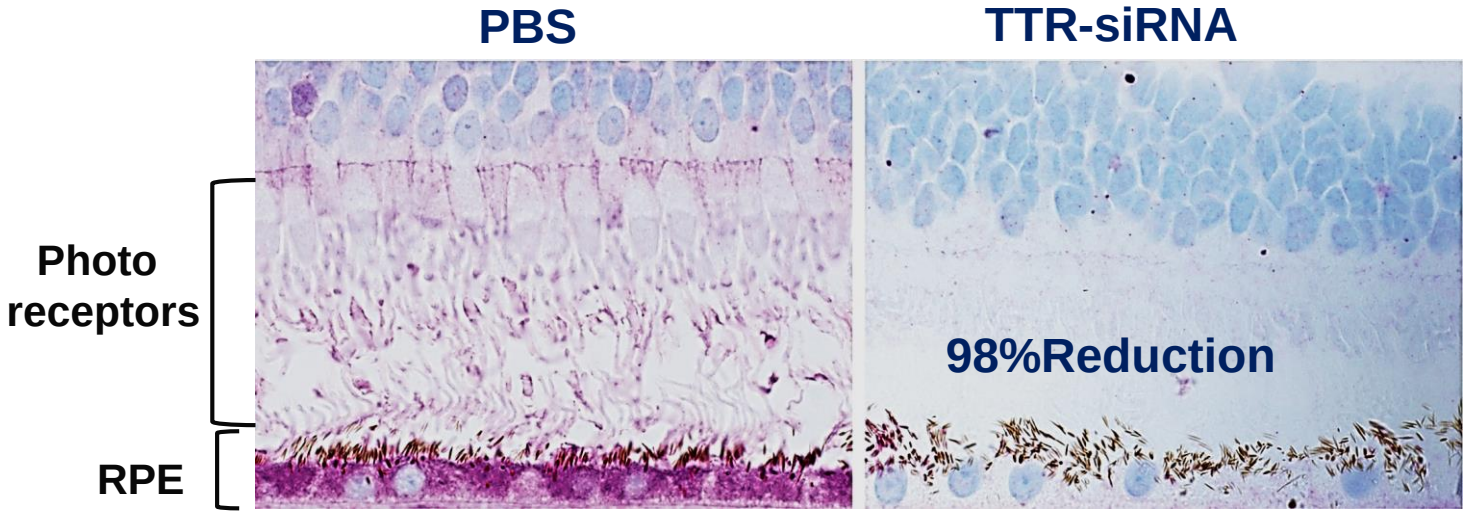
- Initial work with TTR target - therapeutic as well as platform development interest

Single Dose Ocular TTR Silencing in NHP

mRNA



Protein



Day 31 post single dose

*Ciliary Epithelia
‡ Retinal Pigment Epithelium

Alnylam PHARMACEUTICALS

Platform Summary

- **Continued evolution of liver platform**
  - ESC+ increases therapeutic index, mitigates off-target effects
- **Technology translates robustly to CNS and Ocular (others tissues likely)**
  - Broad distribution of silencing in CNS and Eye
  - >90% reduction CNS and Eye
  - Potency and extended duration of liver observed in other tissues
- **Modular and reproducible platform applicable to new therapeutic areas**

Next Wave Programs

Akshay Vaishnaw, M.D., Ph.D.

President, Research & Development

Alnylam PHARMACEUTICALS

Next Wave Strategic Approach

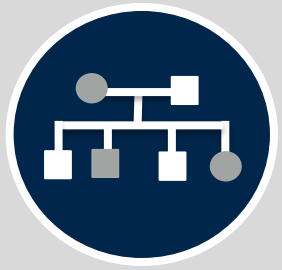
- **Maintain focus on…**
  - Genetically validated targets
  - High unmet need diseases
  - Tractable clinical development path
  - Significant commercial opportunity

- **Continue to build liver portfolio utilizing industry-leading GalNAc conjugate platform**
  - Additional genetic medicines for orphan and ultra-orphan disorders
  - Enter large indications

- **Expand beyond liver**
  - CNS
  - Eye

- **Execute on productivity of 2-3 INDs per annum**

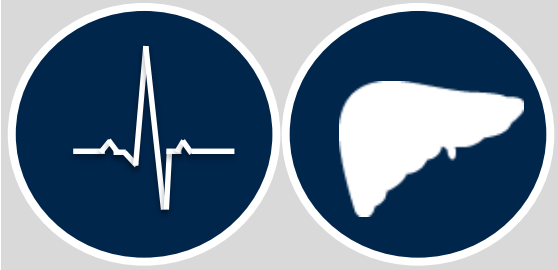
Genetic Medicines



ALN-AAT02

ALN-LEC

Cardio-Metabolic & Hepatic Infectious Diseases



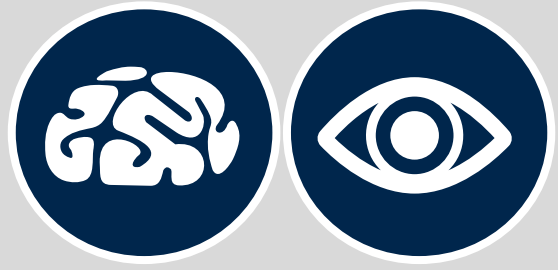
ALN-HBV02^

ALN-AGT

ALN-F12

ALN-HSD*

CNS & Ocular Diseases



ALN-APP

*in partnership with Regeneron Pharmaceuticals

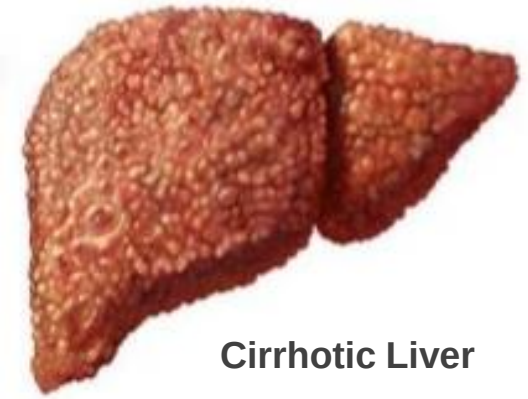
^in partnership with Vir Biotechnology as VIR-2218

Alpha 1 Antitrypsin (AAT) Deficiency Liver Disease

Background

AAT

- Abundant plasma protein (serpin) inhibits neutrophil elastase, primarily synthesized in hepatocytes



Cirrhotic Liver

AAT Deficiency

- Homozygosity for ‘z’ allele (Glu342Lys), PiZZ, accounts for 95% of AAT-deficient patient population
- Prevalence of ZZ homozygosity in U.S. estimated at ~ 1 in 5000

Clinical Features

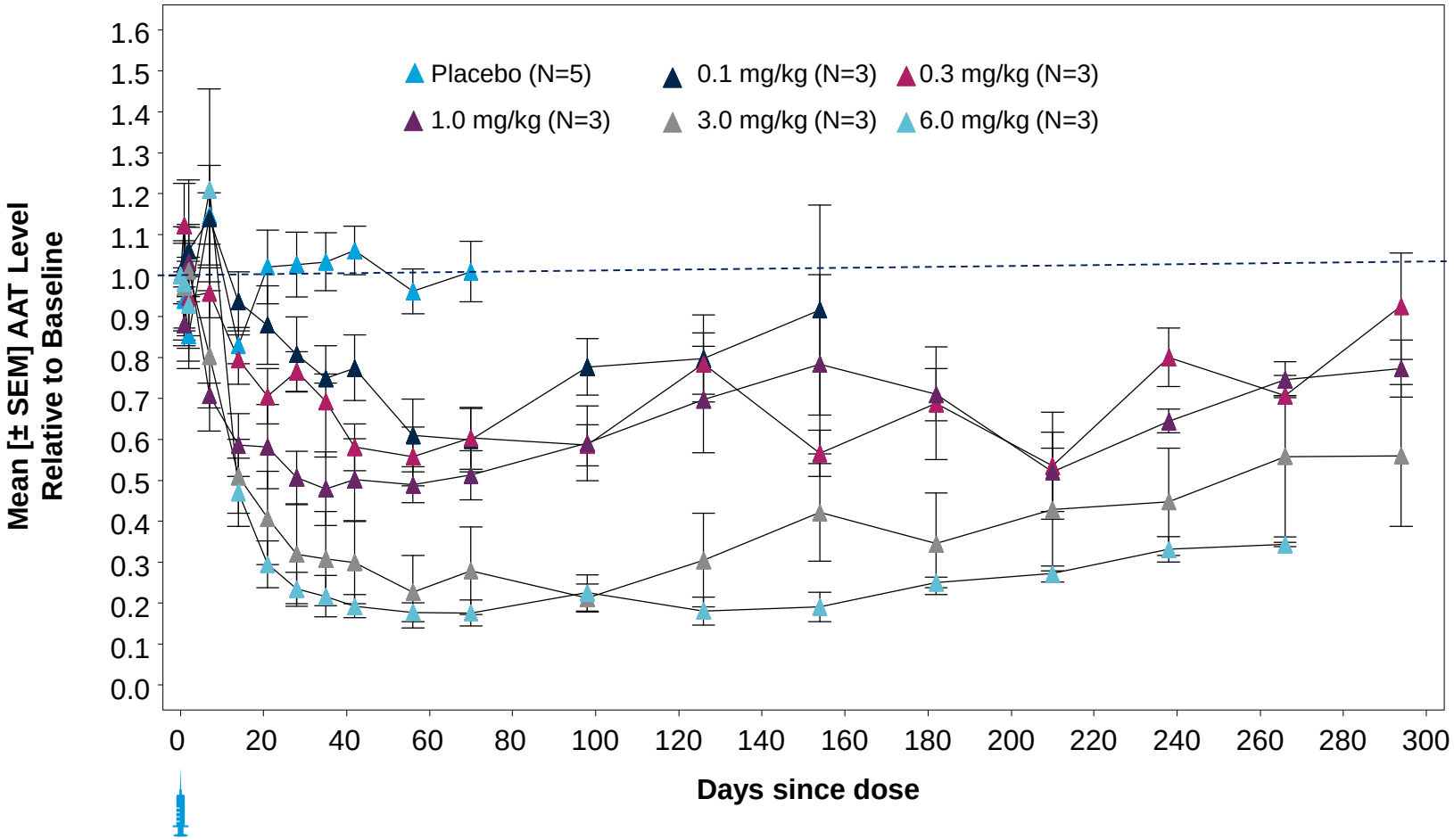
- PiZZ misfolded protein traps in hepatocyte endoplasmic reticulum causing
  - Peripheral deficiency
    - Lack of protease inhibition primarily manifests as lung disease: early onset emphysema
  - Hepatocyte accumulation results in ***liver disease*** – hepatic toxic gain of function presenting as
    - Infantile cholestatic hepatitis
    - Adolescence/adulthood; progressive liver fibrosis progressing to cirrhosis, Can lead to HCC

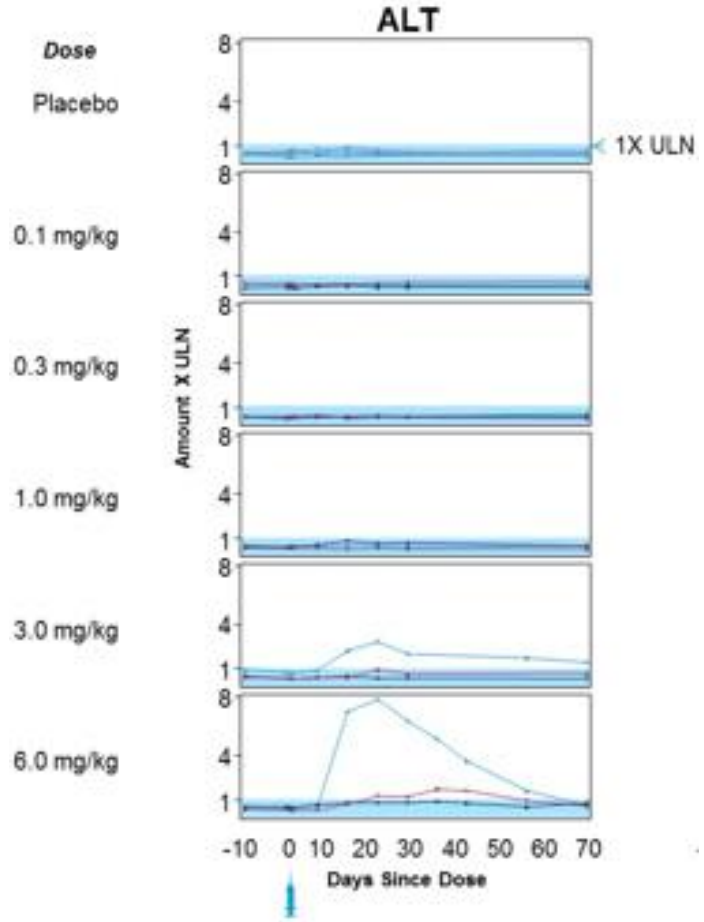
Unmet Need

- No specific therapies exist

ALN-AAT01 ESC GalNAc Conjugate Targeting AAT

Potent, Durable Knockdown of AAT but Transient, Dose-Dependent, Asymptomatic Increase in LFTs





Haslett et al., OTS, September 2016

ALN-AAT02

Summary

- **Alnylam's 1st ESC+ molecule to enter clinic, containing GNA substitution in seed region of antisense strand**
  - ALN-AAT02 has same sequence as ALN-AAT01, but with GNA substitution
- **Clinical liver signal associated with ALN-AAT01 is hypothesized to result from RISC-mediated off-target activity**
  - ESC+ chemistry designed to minimize off-target hybridization while maintaining activity against therapeutic target
- **CTA submitted Oct 2018; approved**
- **Safety and PD data from single ascending dose portion of trial expected in 2019**

LECT2 Amyloidosis (ALECT2)

Background

LECT2

- Abundant plasma protein, potential neutrophil chemotactic factor, primarily synthesized in hepatocytes

ALECT2

- Associated with homozygosity for I58V, 4th commonest cause of systemic amyloidosis after AL, ATTR, and AA
- Ethnic predisposition Hispanic (90% cases in US), Native America, Canadian First Nation, Punjabi, Pakistani, and Egyptian

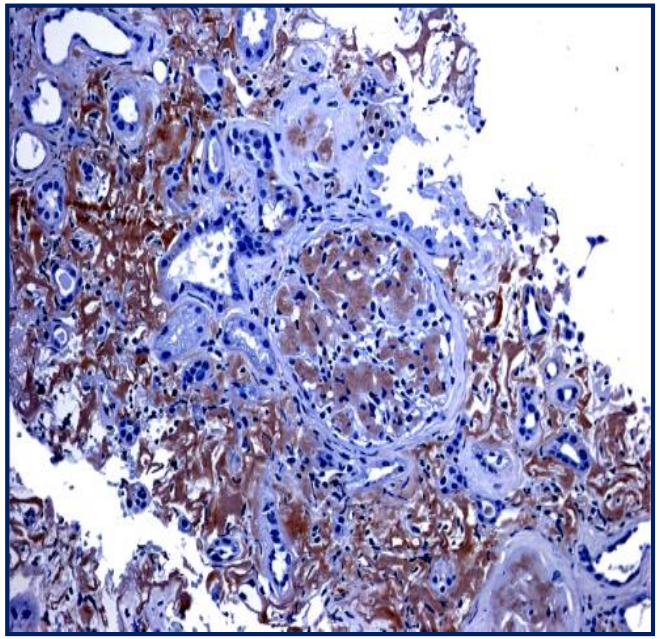
Clinical Features

- Median age at diagnosis 65 (33-88) yrs
- Primarily renal involvement → Chronic kidney disease (CKD) leading to renal failure
- Can involve liver, spleen, lung, adrenal glands
- No obvious extrarenal disease manifestation reported to date

Unmet Need

- No specific therapies exist

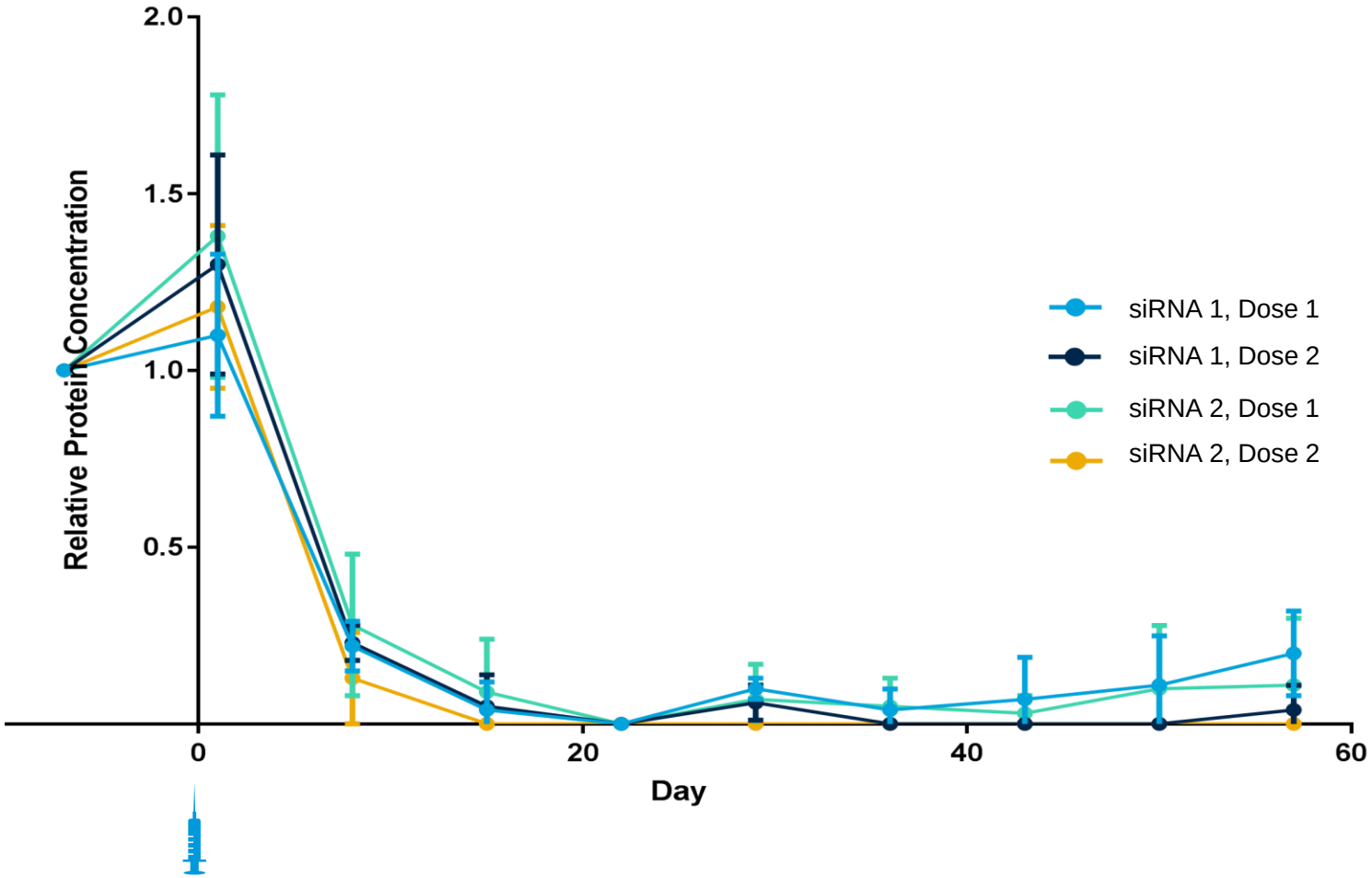
Renal amyloid on biopsy stained with anti-LECT2 (Larsen, KI, 2014)



Alnylam PHARMACEUTICALS

Potent and Durable LECT2 Knockdown Achieved in NHP

Approximately 90% Knockdown After Single Dose



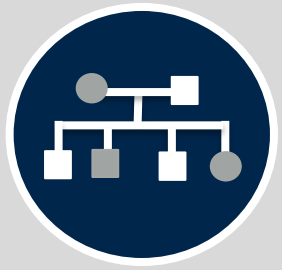
Highly Durable Knockdown Supportive of Once Quarterly Dosing Regimen

ALN-LEC

Summary

- **Recently described form of renal amyloidosis; majority of U.S. cases in patients of Hispanic/Mexican ethnicity**
  - Renal LECT-2 amyloid deposition results in renal failure
- **Therapeutic hypothesis similar to ONPATTRO in hATTR amyloidosis**
  - ALN-LEC designed to reduce hepatic secretion of LECT2, preventing deposition of amyloid fibrils and progression to renal failure
- **Preclinical data demonstrates potent and durable knockdown (~90% KD, single dose, 2 months) in non-human primates**
- **Preclinical development ongoing**
- **Initiating natural history study to measure progression of renal disease**

Genetic Medicines



ALN-AAT02

ALN-LEC

Cardio-Metabolic & Hepatic Infectious Diseases

ALN-HBV02^

ALN-AGT

ALN-F12

ALN-HSD*

CNS & Ocular Diseases

ALN-APP

*in partnership with Regeneron Pharmaceuticals

^in partnership with Vir Biotechnology as VIR-2218

Alnylam PHARMACEUTICALS

Hepatitis B Virus (HBV)

HBV

- Member of hepadnavirus family
- Transmitted via blood and sexual contact

Acute Infection (virus cleared)

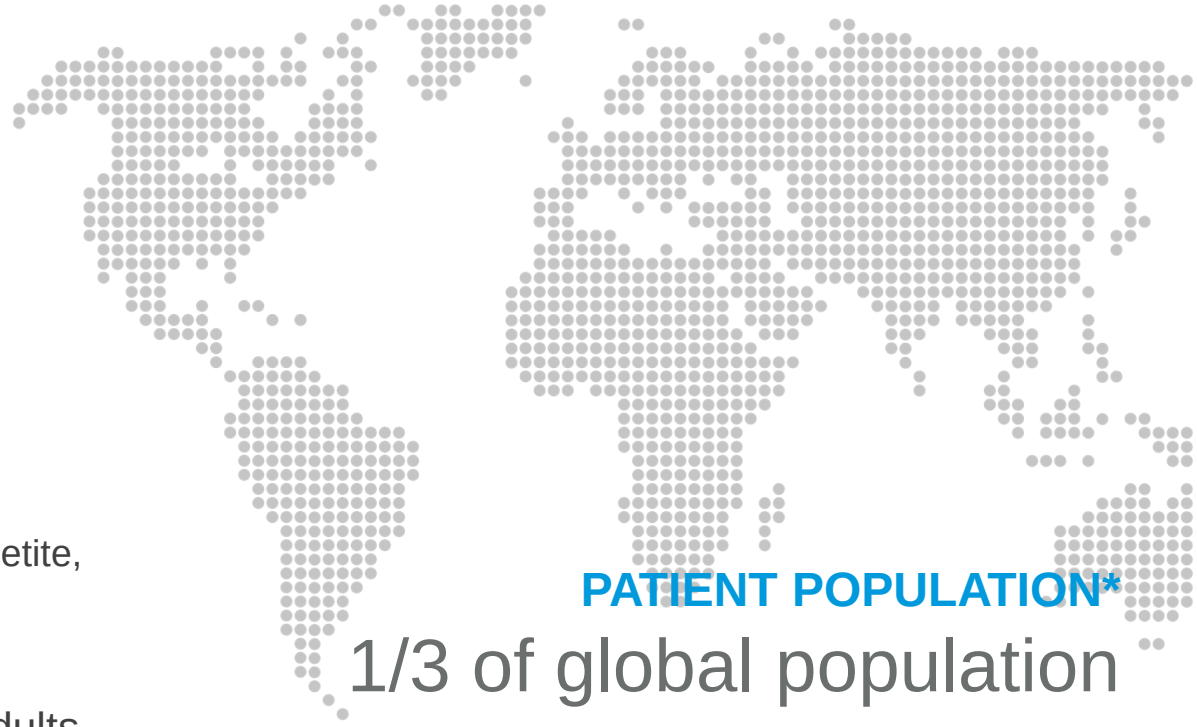
- Asymptomatic
- Symptomatic
  - Commonly associated with transient acute viral hepatitis; loss of appetite, nausea, vomiting, fever, and jaundice

Chronic Infection (virus persists)

- Seen most commonly in infants (transmitted from mother) > adults
- Chronic infection
  - Asymptomatic, or
  - Symptomatic with progressive chronic hepatitis with potential for cirrhosis
- Individual is infectious and can transmit virus

Unmet Need

- Existing antiviral treatments suppress viral load but do not cure



PATIENT POPULATION*

1/3 of global population exposed

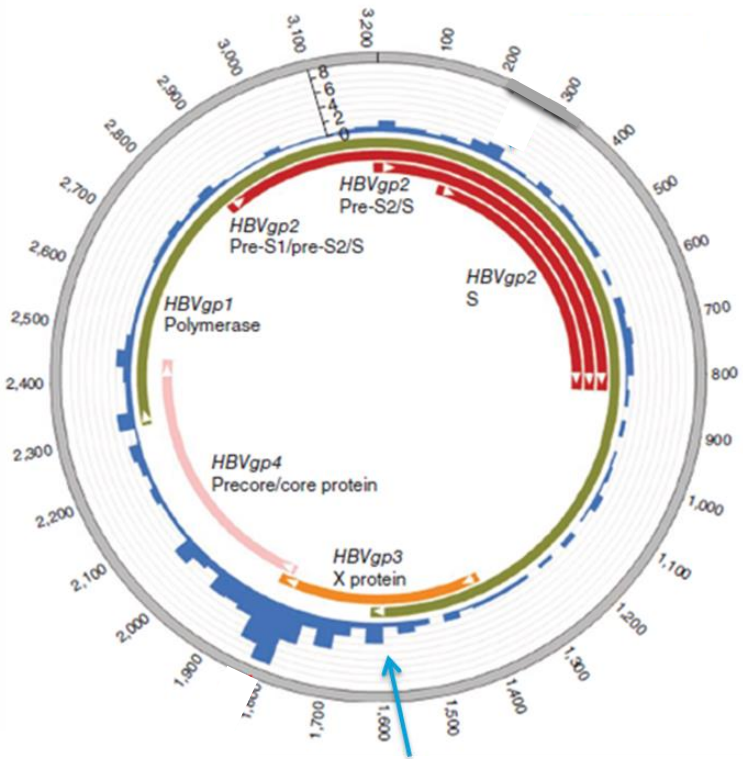
~290M patients worldwide

25M worldwide with chronic infection

Schweitzer et al. Lancet 386:1546-1555, 2015; Basnayake, S.K. and Easterbrook, P.J., J. Viral Hepatitis 23: 545-559, 2016

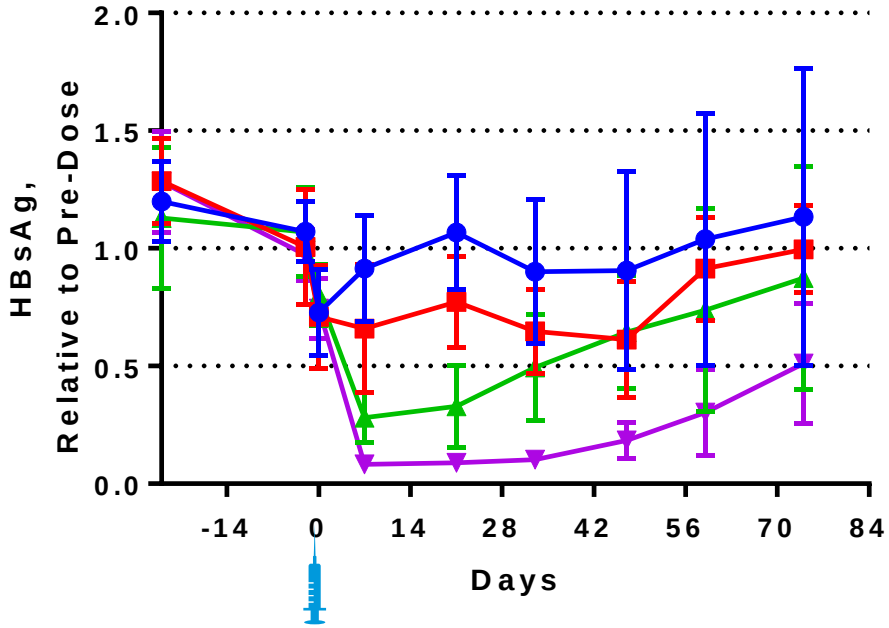
ALN-HBV02 (VIR-2218) Targets Highly Conserved Sequence in HBV X Orf

- Target site conserved across genotypes A-J
  - Perfect homology (2-18): 97.2%. Allow 1 mismatch: 99.7%
- Site upstream from integration hotspot



ALN-HBV02 (VIR-2218)

- Potent and durable activity in AAV-HBV murine model
- Circulating HBsAg levels after single SC injection of ALN-HBV02 (VIR-2218)



ALN-HBV02 (VIR-2218)

Summary

- **RNAi based anti-HBV approach designed to inhibit expression of all HBV proteins, including HBsAg**
  - Targets highly conserved sequence
  - Shown to cause multi-log reduction in HBsAg
- **ALN-HBV02 (VIR-2218) is 1st ESC+ molecule to start dosing in humans**
  - Designed to maintain on-target activity but reduce off-target effect
- **Vir-led Phase 1/2 trial evaluating safety, tolerability, pharmacokinetics, and antiviral activity of ALN-HBV02 currently underway**
- **Topline data expected in 2019**

Hypertension

Hypertension

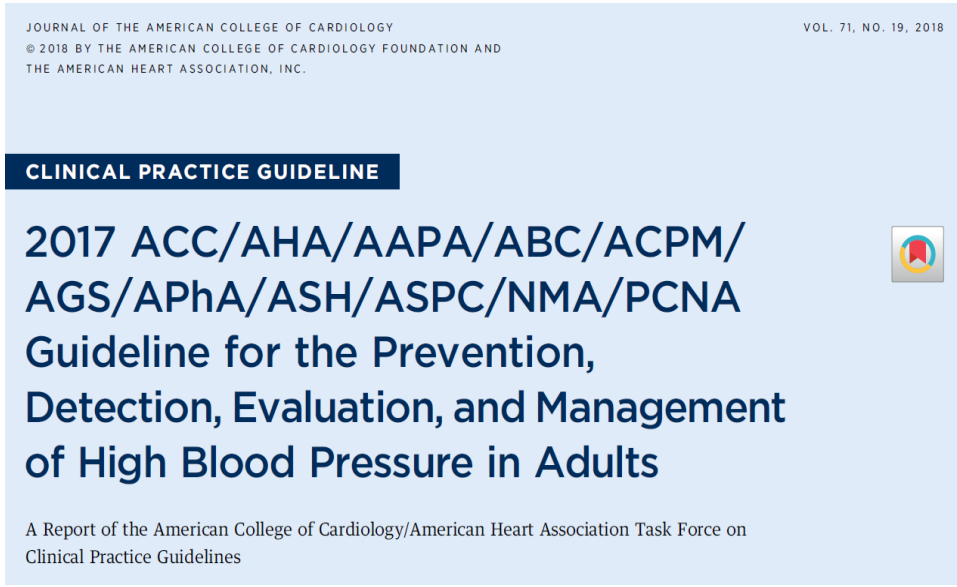
- Complex multifactorial disease
  - >100 genetic loci implicated
  - Diet (salt), weight and lifestyle contribute
- Defined as systolic blood pressure (SBP)>130, or diastolic blood pressure (DBP)>80mmHg

Clinical Features

- Asymptomatic, but over 30 years of age, risk of CV disease increases in a log-linear fashion from SBP levels 115-180 mmHg and DBP levels 75-105 mmHg

Unmet need

- 45.6% of U.S. adults have hypertension under 2017 ACC/AHA guidelines, with more than half of patients on medication remaining above BP target
- Despite availability of antihypertensives
  - Poor adherence rates
  - Peak/trough effects
  - Resistant and refractory hypertension
  - In 2015, high BP leading cause of death and disability-adjusted life years worldwide

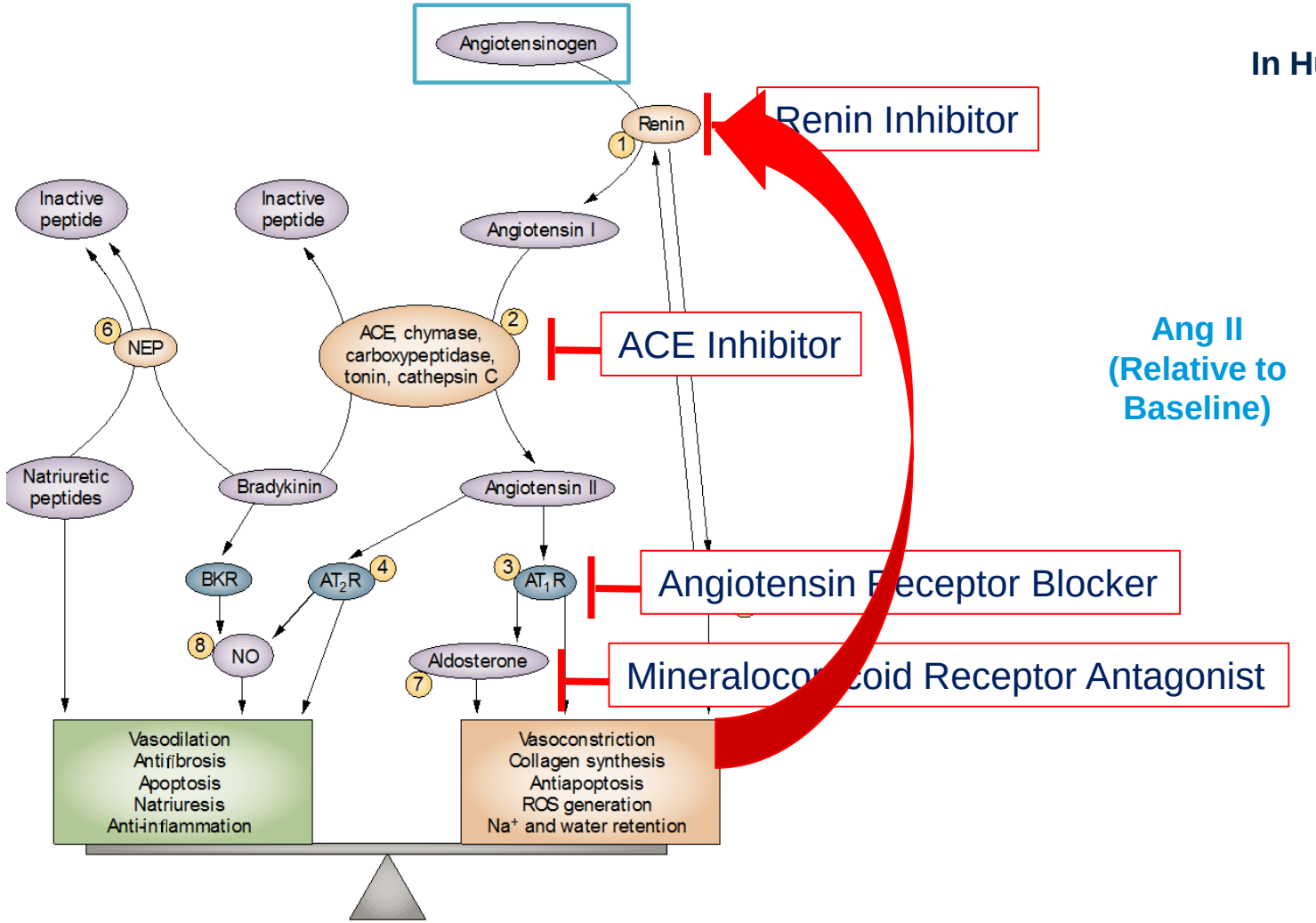


1Lim SS, Vos T, Flaxman AD, et al. 2010. Lancet. 2012;380:2224-60. 2Danaei G, Ding EL, Mozaffarian D, et al. PLoS Med. 2009;6:e1000058. 3Willey JZ, Moon YP, Kahn E, et al. J Am Heart Assoc. 2014;3:e001106. 4Saran R, Li Y, Robinson B, et al. Am J Kidney Dis. 2015;66 Svii:S1-305 5Wilson PW, Kannel WB, Silbershatz H, et al. Arch. Intern. Med. 1999; 159:1104-9. 6Vital signs: awareness and treatment of uncontrolled hypertension among adults-United States, 2003-2010 CDC 2012; AHA (www.heart.org). 7.HTN: Muntner P et al, Circulation 2017 [Pubmed 29133599]. 8. Forouzanfar MH et al, Lancet 2016 [Pubmed ID 27733284]

Alnylam PHARMACEUTICALS

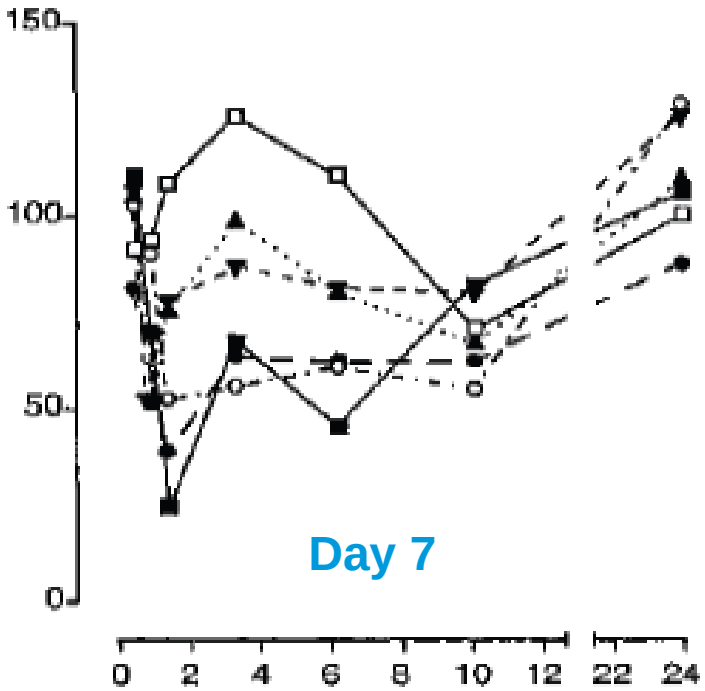
Renin-Angiotensin System

Angiotensinogen, a Validated Target for Hypertension



Zhou, Nature (2010)

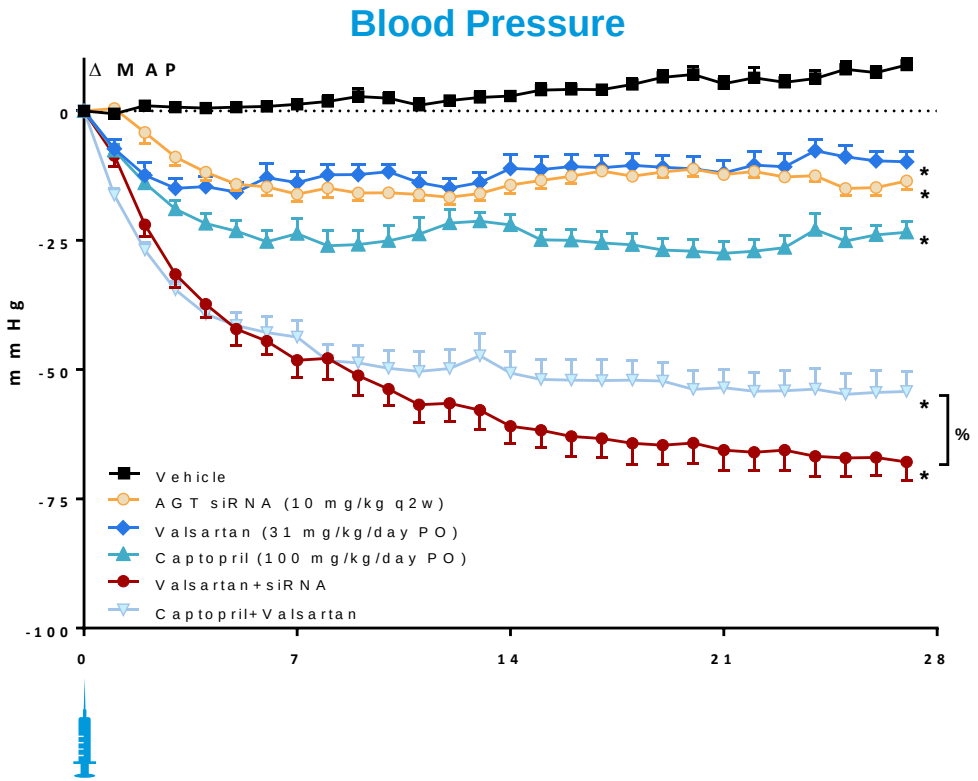
Evidence of Ang II Escape In Humans After Renin Blockade With Aliskiren



Nussberger, Hypertension (2002)

ALN-AGT for Hypertension

Angiotensinogen Silencing Results in BP Lowering in Rat Hypertension Model



- AGT siRNA reduced BP
- Combination of AGT siRNA and valsartan resulted in synergistic BP reduction, greater than captopril and valsartan
  - Well tolerated, with no decrease in eGFR
- Only AGT siRNA plus valsartan normalized cardiac hypertrophy

ALN-AGT

Summary

- **Hypertensive disorders are leading preventable causes of death**
  - Prevalence of high blood pressure, its complications, and related mortality rising
  - New 2017 ACC/AHA guidelines dramatically increase size of target population

- **AGT silencing represents novel approach for treatment of hypertension**
  - Angiotensinogen silencing in spontaneous hypertensive rat leads to decrease in BP
    - Clamped inhibition of renin-angiotensin pathway
    - Reduced angiotensin II escape due to depletion of substrate
    - Combination treatment with angiotensin II receptor blockers (ARB) results in synergistic blood pressure reduction
  - Single dose ALN-AGT in normotensive non-human primate shows excellent translation: knockdown, lowered BP and durability

- **ALN-AGT ESC+ molecule expected to enter clinic in 2019**
  - Multiple laboratory (renin, angiotensin I, II) and clinical (BP) biomarkers

Thromboembolism

Thrombotic Disease

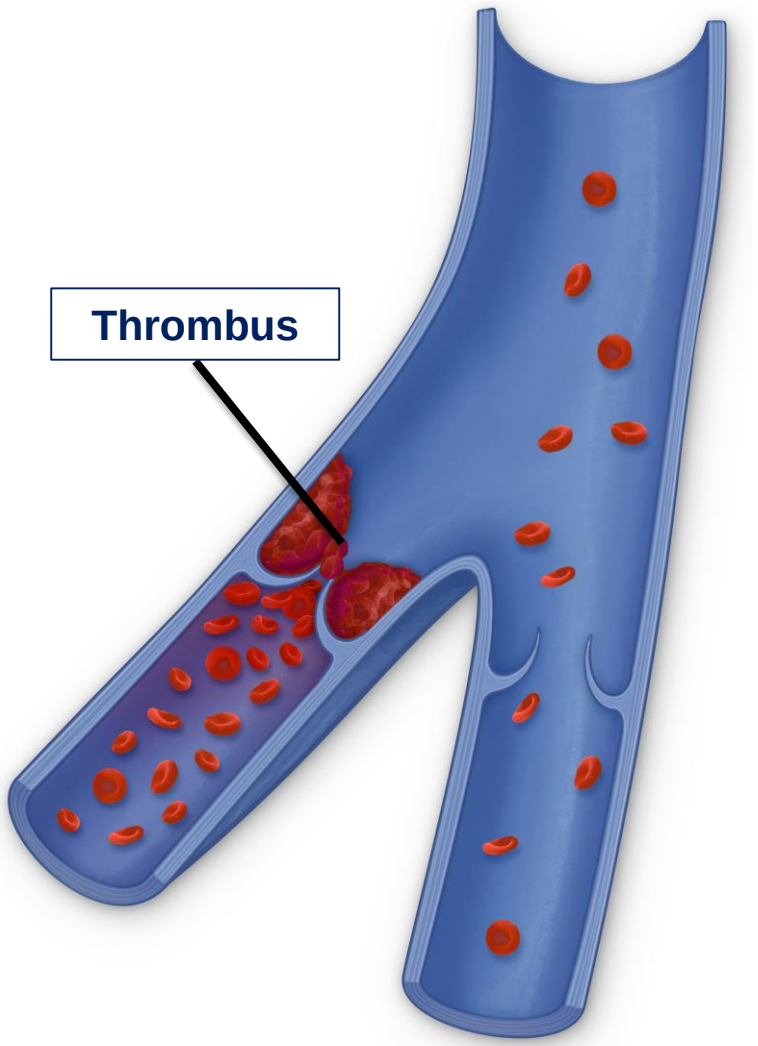
- Thrombotic disorders are major source of morbidity and mortality
  - Mutlifactorial etiology: genetic and environmental

Clinical Features

- Arterial
  - Ischemia, infarction, e.g., ACS, stroke
  - Secondary to arrhythmias, e.g., AF
  - Associated with valvular implants
- Venous
  - DVT, PE including after orthopedic surgery, post op, or convalescence

Unmet Need

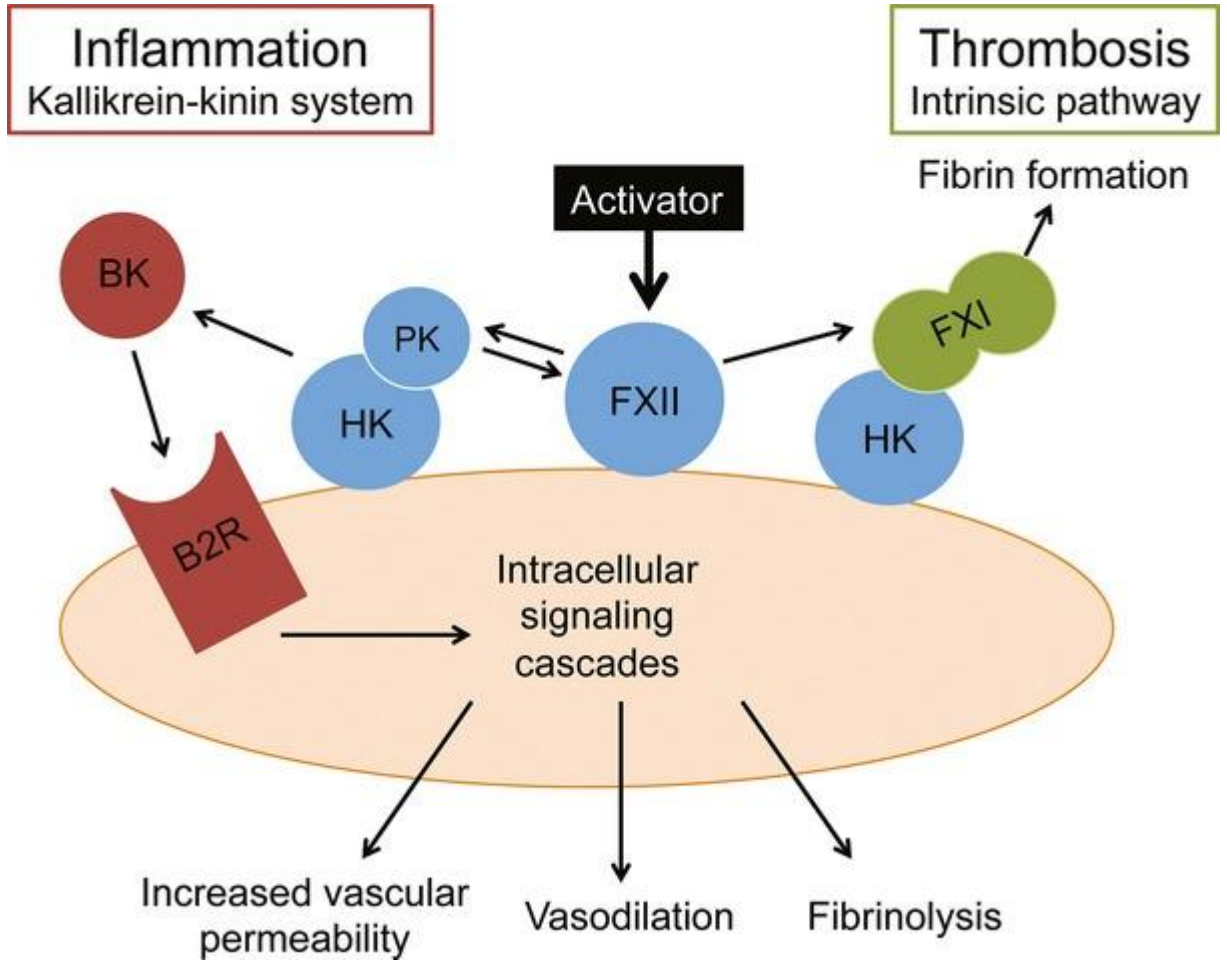
- Many underserved high risk populations
  - End-stage renal disease on hemodialysis: U.S. ~ 0.5 million
  - Atrial fibrillation with mechanical heart valve: U.S. ~350,000
  - Cancer-associated thrombosis: U.S. ~250,000
- Ideal product profile for thrombophylactic agent
  - Effective, convenient AND safe with no increased bleeding risk
    (all current therapies, including Xa inhibitors associated with bleeding risk)



Intersection of Coagulation and Kininogen Pathways

FXII, a Genetically Validated Target in Thrombosis Prevention

- FXII is serine protease activated by contact with negatively charged surfaces
  - PROCOAGULANT: Activation of intrinsic clotting pathway
  - PROINFLAMMATORY: Activation of kallikrein/bradykinin system
- Homozygous FXII deficiency not associated with disease (Hageman trait)
  - Increased APTT without bleeding risk
- Therapeutic hypothesis
  - Reduction in FXII will prevent thrombosis but not increase risk of bleeding

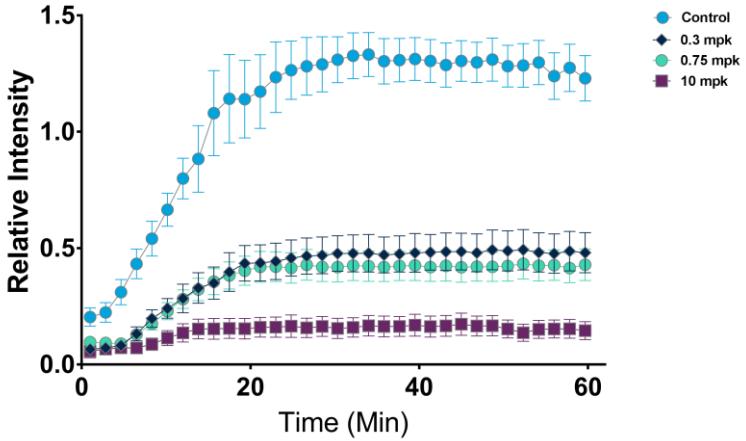


Kenne et al, J. Int Med. 278:571 (2015)

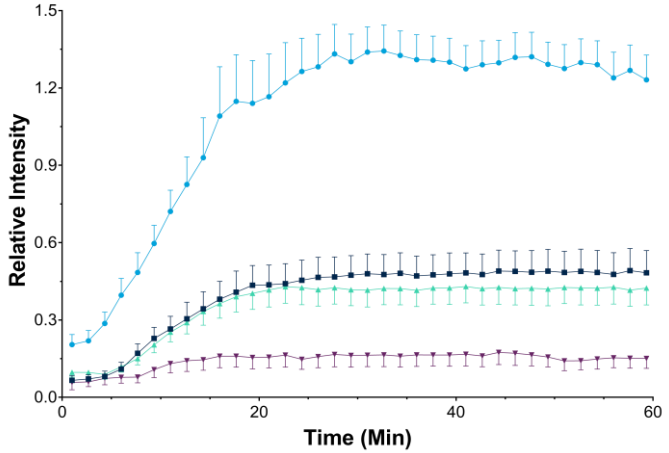
ALN-F12 for Thromboprophylaxis

ALN-F12 inhibits venous thrombosis in rodents

Platelet Deposition (ALN-F12)



Fibrin Deposition (ALN-F12)



Liver mRNA

100% F12 (Control)

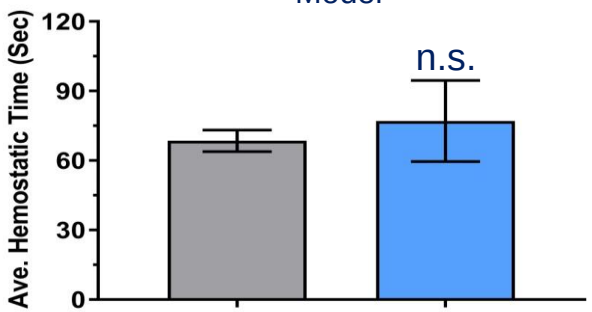
48% F12

25% F12

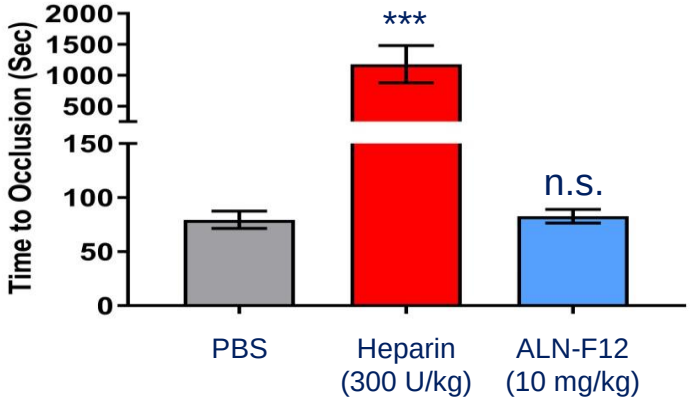
3% F12

FXII reduction by ALN-F12 does NOT impair hemostasis in rodents

Saphenous Vein Bleeding Model



Tail Tip Transection Model



ALN-F12

Summary

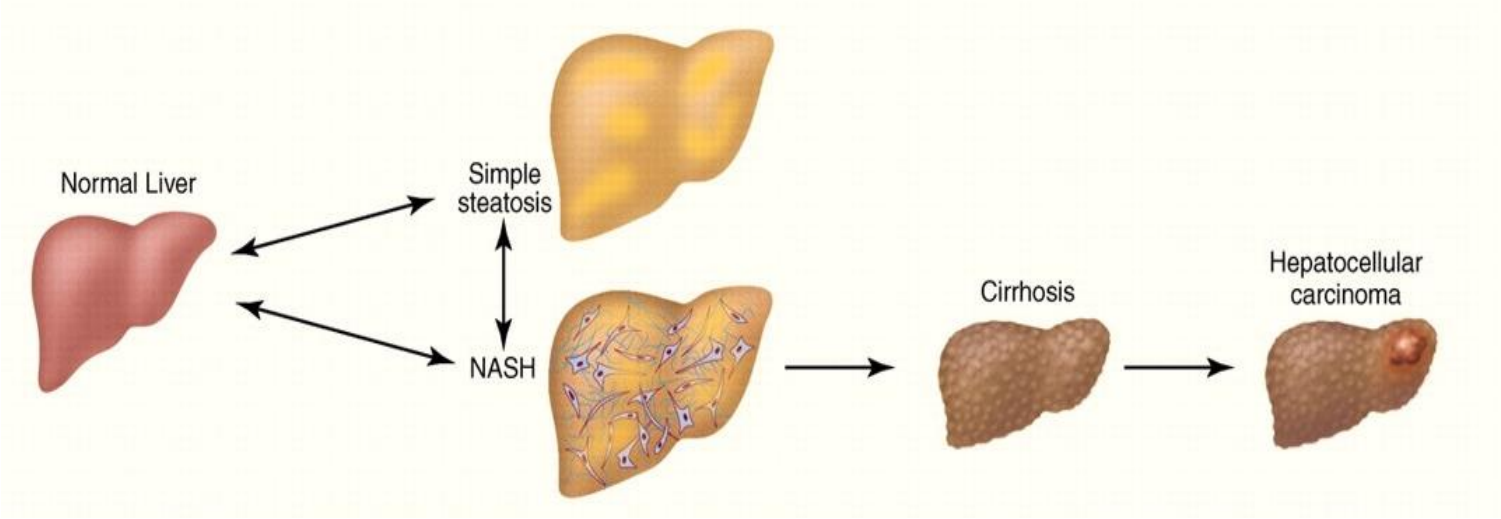
- **Thrombotic disorders are major cause of morbidity and mortality**
  - Some significant high unmet need populations (renal, heart valve-related and cancer) where safe and effective thromboprophylaxis challenging
- **FXII silencing represents novel approach for thromboprophylaxis**
  - ALN-F12 prevents thrombosis without increased bleeding risk in rodent models of thrombosis and hemostasis
  - Consistent data in rodents and NHPs
- **ALN-F12 is IND ready**
  - Multiple laboratory (FXII, APTT) and clinical (bleeding time) biomarkers

Non-Alcoholic Steatohepatitis (NASH)

REGENERON
science to medicine®

Non-Alcoholic Fatty Liver Disease (NAFLD)

- Leading cause of liver disease globally
  - Defined as excess liver fat in absence of other causes
  - Major risk factors; obesity, type 2 diabetes mellitus and metabolic syndrome



Clinical Features

- NAFL (steatosis only), or
- **Non-alcoholic steatohepatitis** (**NASH**)
  - Steatosis accompanied by inflammation and ballooning
  - NASH frequently progresses to liver fibrosis

Unmet Need

- NASH is predicted to be major driver for liver transplantation by 2020
- Liver-related mortality increased exponentially with fibrosis progression
- Urgent need for disease-modifying therapies

[1]Cohen et al. Science 2011; 332-1519
[2]Estes et al. Hepatology. 2018;67(1):123

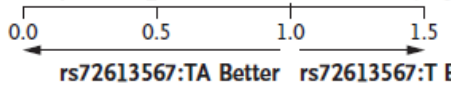
Alnylam PHARMACEUTICALS

HSD17B13: Loss-of-Function Mutation that Protects Against NASH

Chronic liver diseases with high unmet need

A GHS Discovery Cohort

Description	Genotype	Case Patients	Controls	Genotypic Odds Ratio (95% CI)	Allelic Odds Ratio (95% CI)	P Value
Alcoholic liver disease (N=190) vs. normal (N=29,928)					0.62 (0.48–0.81)	1.8×10^{-4}
	T/T	128	16,084	1		
	T/TA	54	11,754	0.58 (0.42–0.80)		
	TA/TA	8	2,090	0.47 (0.23–0.97)		
Alcoholic cirrhosis (N=124) vs. normal (N=29,928)					0.56 (0.41–0.78)	3.4×10^{-4}
	T/T	85	16,084	1		
	T/TA	36	11,754	0.58 (0.39–0.86)		
	TA/TA	3	2,090	0.27 (0.09–0.85)		
Nonalcoholic liver disease (N=1857) vs. normal (N=29,928)					0.84 (0.78–0.91)	1.3×10^{-5}
	T/T	1090	16,084	1		
	T/TA	665	11,754	0.83 (0.75–0.92)		
	TA/TA	102	2,090	0.70 (0.57–0.87)		
Nonalcoholic cirrhosis (N=374) vs. normal (N=29,928)					0.74 (0.62–0.88)	4.8×10^{-4}
	T/T	231	16,084	1		
	T/TA	127	11,754	0.74 (0.60–0.93)		
	TA/TA	16	2,090	0.51 (0.31–0.85)		
Hepatocellular carcinoma (N=75) vs. normal (N=29,928)					0.67 (0.45–1.00)	0.047
	T/T	49	16,084	1		
	T/TA	23	11,754	0.65 (0.39–1.06)		
	TA/TA	3	2,090	0.48 (0.15–1.56)		



HSD17B13 is thus an attractive target for the treatment of NASH and other chronic liver diseases

Protective allele (TA) significantly reduces prevalence of NASH, ASH, cirrhosis and HCC

[1]Abul-Husn et al. NEJM 2018 378;12, 1096
[2]Estes et al. Hepatology. 2018;67(1):123
Pirola et al, J Lipid Rs, 2018

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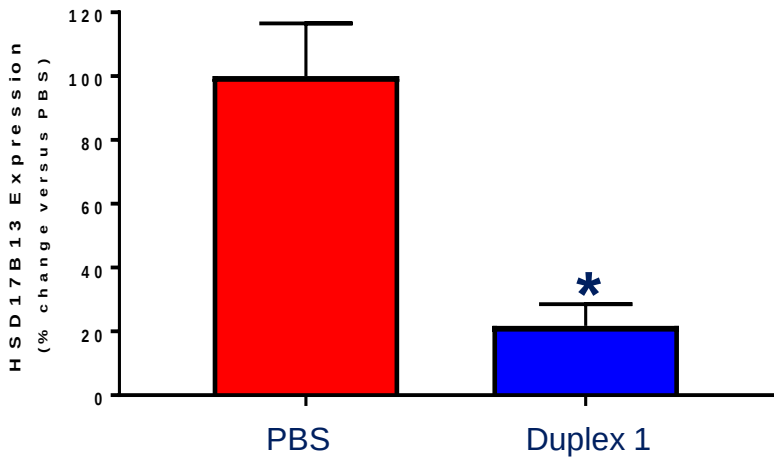
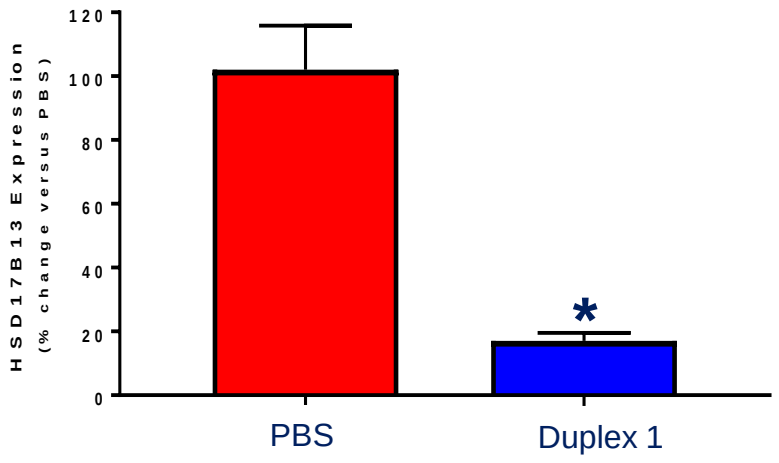
Development of RNAi Therapeutic Against Hepatic HSD17B13

Validation of Early Lead Candidate *In Vivo*

Human/NHP cross-reactive siRNA: Efficacy against ectopically expressed human HSD17B13 in mice



Human/NHP cross-reactive siRNA: Efficacy against endogenous HSD17B13 in non-human primates



Optimization and DC selection ongoing

ALN-HSD

Summary

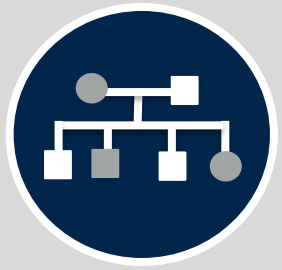
- **Non-alcoholic steatohepatitis (NASH) arising as major global liver disorder, predicted to be major driver of liver transplants**

- **Naturally occurring loss-of-function genetic variant in HSD17B13 associated with reduced risk of chronic liver diseases, including NASH**
  - Hepatocyte expressed intracellular target amenable to RNAi therapeutics
  - Silencing potentially mimics loss-of-function genetic variant
    - Based on genetic studies, ≥50% silencing of HSD17B13 anticipated to lead to clinical benefit

- **Selection of Development Candidate ongoing; Potential 2020 IND**

[1]Cohen et al. Science 2011; 332-1519
[2]Estes et al. Hepatology. 2018;67(1):123

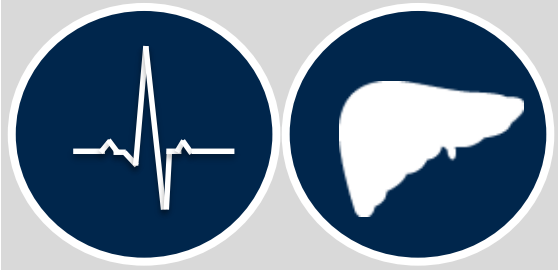
Genetic Medicines



ALN-AAT02

ALN-LEC

Cardio-Metabolic & Hepatic Infectious Diseases



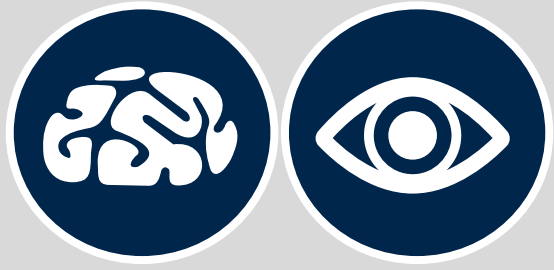
ALN-HBV02^

ALN-AGT

ALN-F12

ALN-HSD*

CNS & Ocular Diseases



ALN-APP

*in partnership with Regeneron Pharmaceuticals
^in partnership with Vir Biotechnology as VIR-2218

CNS Target Landscape

Illustrative Table of Potential RNAi Therapeutics Targets

Target	Inheritance	Disease	Target location	Biomarkers
Huntingtin (Htt)	Autosomal dominant	Huntington's	Striatum and cortex	CSF Htt mRNA and protein
α- synuclein (SNCA)	Autosomal dominant	Parkinson's	Substantia nigra, medulla oblongata	CSF SNCA mRNA and protein
Ataxin-2 (ATXN2)	Autosomal dominant	- Spinocerebellar ataxia type 2 - Amyotrophic lateral sclerosis	Spinal cord, brainstem, cerebellum	CSF ATXN2 mRNA and protein
Tau	Autosomal dominant	- Frontotemporal dementia 17 - Progressive supranuclear palsy	Fronto-temporal cortex	CSF tau mRNA and protein
SOD-1	Autosomal dominant or recessive	Amyotrophic lateral sclerosis	Spinal cord	CSF SOD-1 mRNA and protein
Others....e.g., APP-CAA				

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Hereditary Cerebral Amyloid Angiopathy (APP-hCAA)

hCAA is Rapidly Progressive Disease Associated with Intracerebral Hemorrhage and Dementia

Amyloid Precursor Protein (APP)

- Integral membrane protein concentrated in neuronal synapses
- Function poorly understood
- Proteolysis releases Aβ fragment

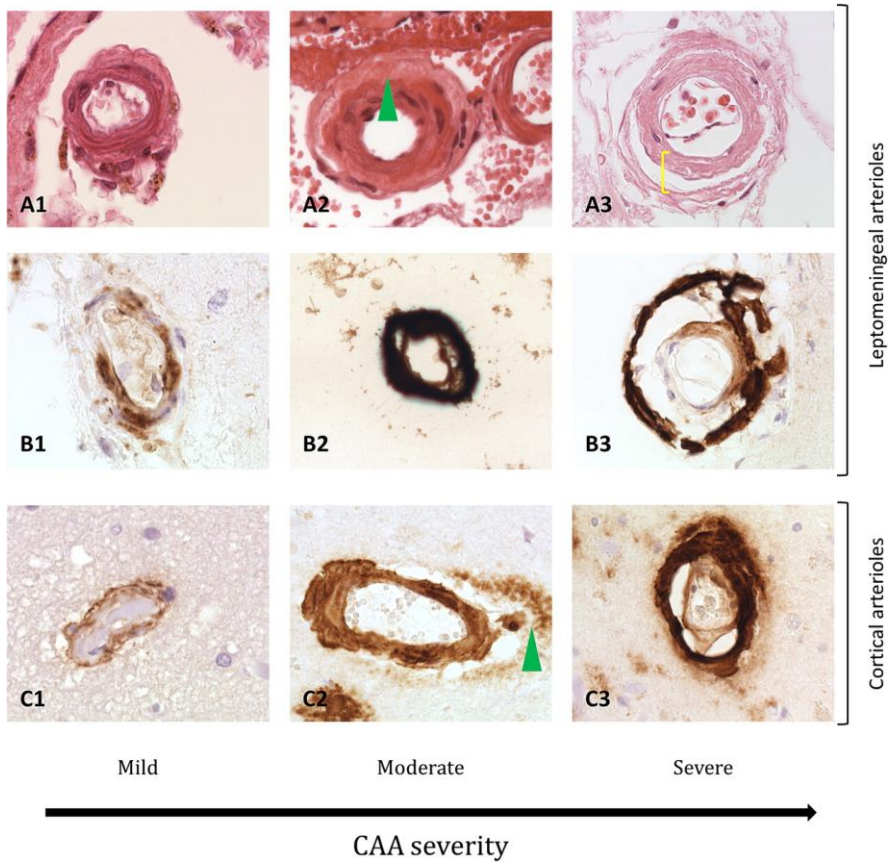
hCAA Genetics

- Hereditary Cerebral Hemorrhage with Amyloidosis–Dutch Type (HCHWA-D)
  - Autosomal dominant APP mutation, E693Q, in several hundred Dutch individuals
  - Other autosomal dominant APP mutations described
- APP copy number variation
  - Trisomy 21
  - Microduplications of Ch 21

hCAA Clinical Features

- Characterized by Aβ amyloid fibril deposition in CNS small vessel walls
- Onset age 35-45; progression from micro-hemorrhages to intracerebral hemorrhage (ICH) within 2-5 years, peak age at death is 55 yrs
- Can result in cognitive defects and dementia
- No known therapies

Vessel Wall Changes in hCAA



1Kamp et. al., Rev. Neuro 2014;83:124-137. 2Rovelet-Lecrux et. al. Nature Genetics 2006;38:24-26. 3Natte et. al., Ann Neurol 2001;50:765-772. 4Greenberg et. al., Curr Opin Neurol 2018;31:28-35. 5Greenberg et. al., Lancet Neurol 2014;4:419-428. 6Charidimou A et al. J Neurol Neurosurg Psychiatry 2012;83:124-137

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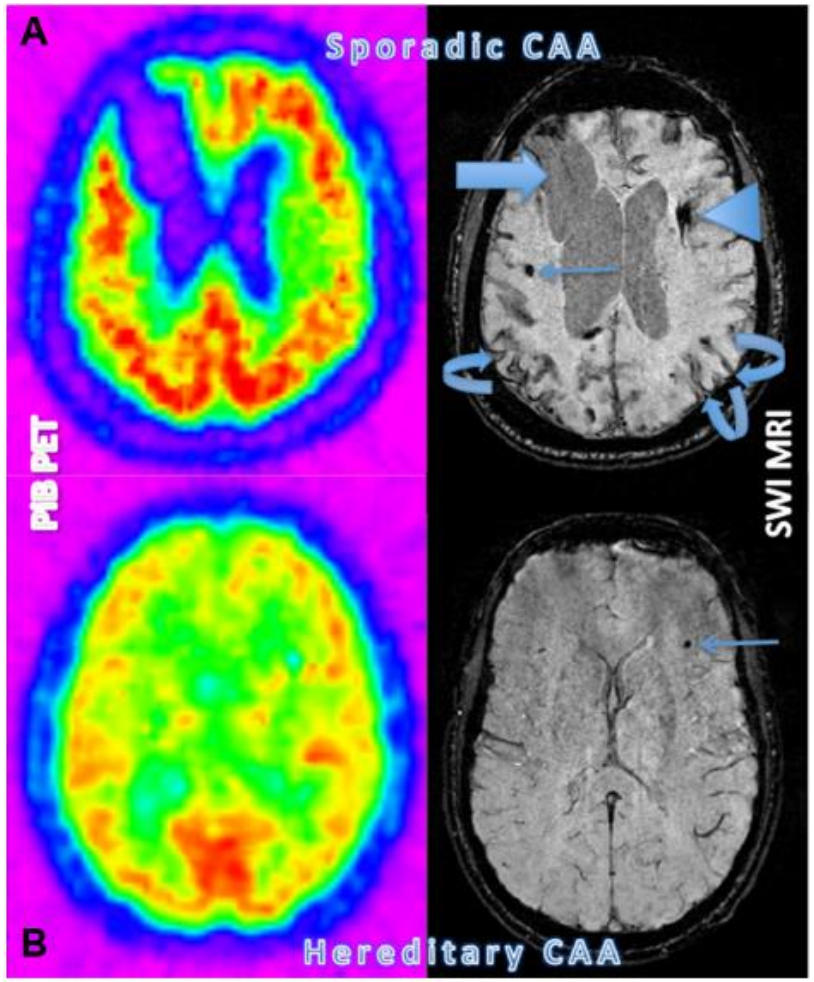
Dutch Type Hereditary CAA is Potential Gateway to Larger CNS Indication

Clinically Proven Approach with Transformational Potential

Significant Similarities Between Inherited and Sporadic CAA



hCAA (Dutch, other)

- Ultra-rare, inherited
- Presents with microbleeds and ICH in middle age
- Establish early POC
  - Dose finding
  - Safety
  - Biomarkers for efficacy

Sporadic CAA

- **<u>~20% of brains at autopsy show CAA</u>**
- Commonest cause of lobar ICH in elderly
  - 86 (36%) of 316 patients developed recurrent ICH over mean follow up time of 5 years
- Clinical efficacy endpoints
  - Microbleeds, ICH, cognitive function

Gurol et al., Stroke. 2016; 47:1146-1152

ALN-APP

Summary

- **Hereditary Cerebral Amyloid Angiopathy (hCAA) caused by mutations in APP protein; leads to arteriolar Aβ fragment deposition**
  - Amyloid deposition causes damage to endothelium resulting in microhemorrhages and ultimately ICH
- **Study of Dutch hCAA population potential gateway to larger indications**
  - E.g., Sporadic CAA
- **Preclinical development ongoing; expected to enter clinic by 2020**
- **Additional CNS programs to be added on annual basis, starting in 2020**

Next Wave Summary

- **Alnylam advancing large number of Next Wave programs, fueling sustainable growth**
  - Expect productivity supporting 2-3 new INDs/yr
- **Early-stage clinical and late-stage pre-clinical programs aimed at both rare and common diseases, and include liver and initial CNS targets**
  - Many additional liver targets being pursued as Genetic Medicines and for Cardio-metabolic and Hepatic Infectious Diseases
  - Significant future opportunity with CNS and ocular delivery
- **Across broad number of disease indications RNAi therapeutics have great promise as new class of medicines for patients!**

Q&A Session #2

12:25 – 12:40

Moderator:

- Yvonne Greenstreet, MBChB, Chief Operating Officer

Panelists:

- Sally-Anne Hulton, M.D., Birmingham Children's Hospital NHS Trust
- Pritesh Gandhi, PharmD., VP & General Manager, Lumasiran
- Kevin Fitzgerald, Ph.D., SVP, Research
- Akshay Vaishnaw, M.D., Ph.D. President, Research & Development

Commercialization Strategy & Closing Statements

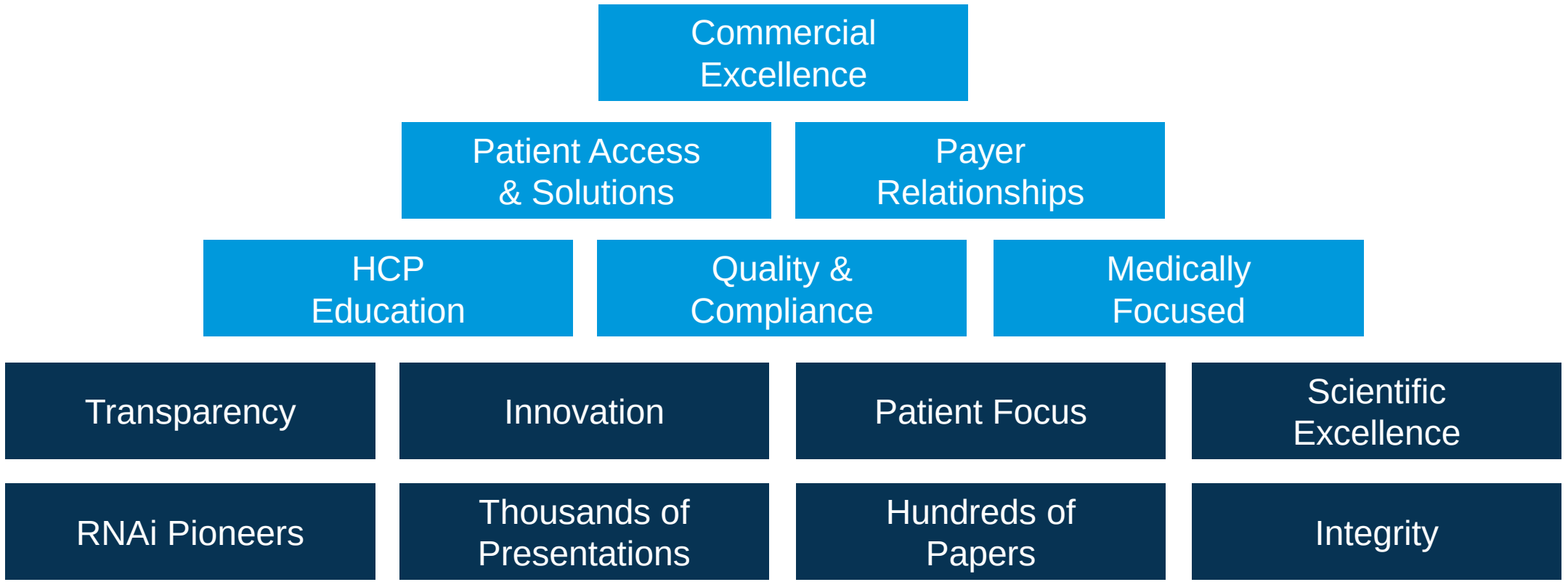
Barry Greene

President

Alnylam® PHARMACEUTICALS

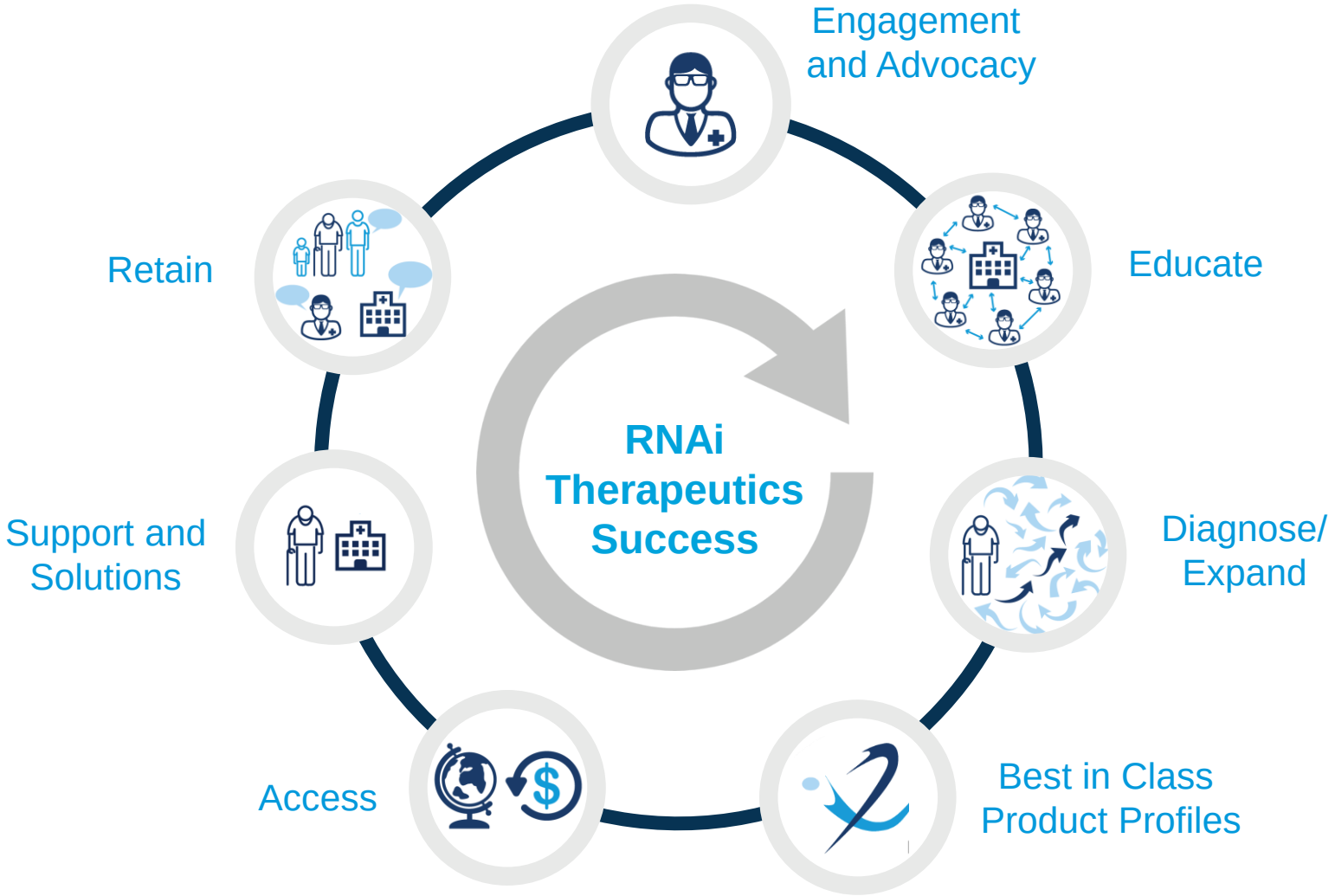
Alnylam's Commercial Transition

Commercial Leaders

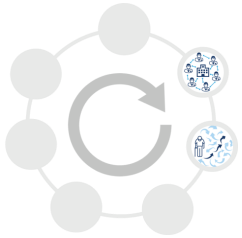


R&D Leaders

Succeeding in Rare Disease Requires a Specific Road Map

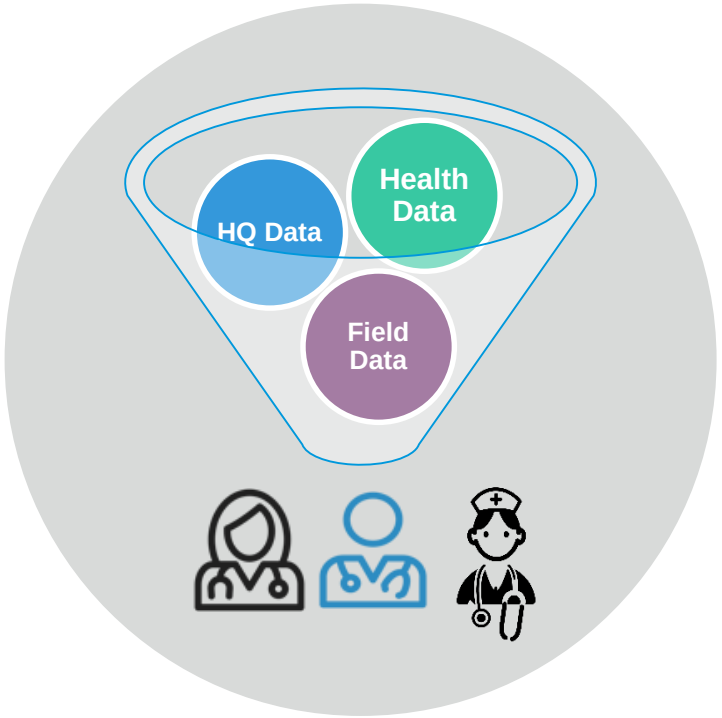


Innovative Approaches to Discover Key Specialists and Patients

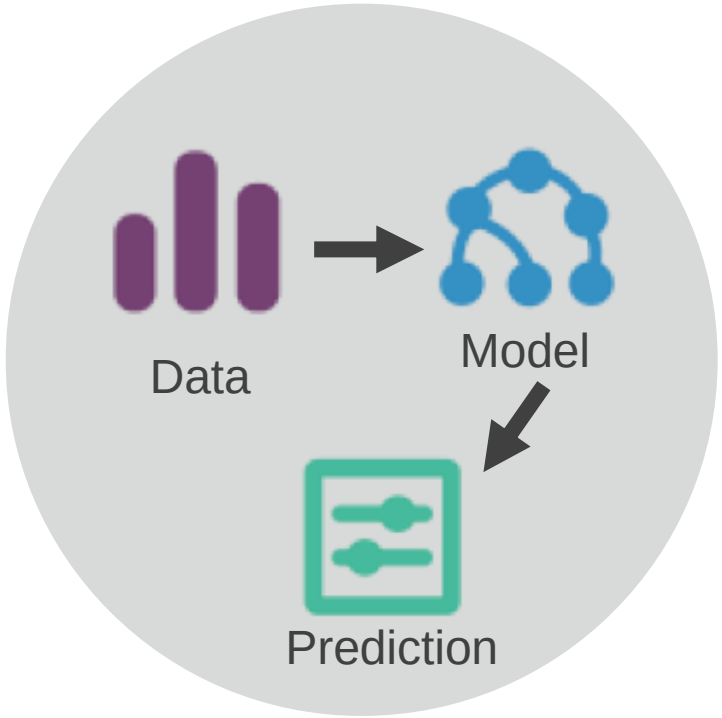


Educate

Diagnose/Expand



Custom HCP Lead Generation and Management Tool



Machine Learning Techniques to support Patient Discovery

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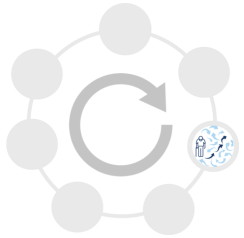
No-Charge Third-Party Genetic Testing and Counseling Program



Diagnose/Expand

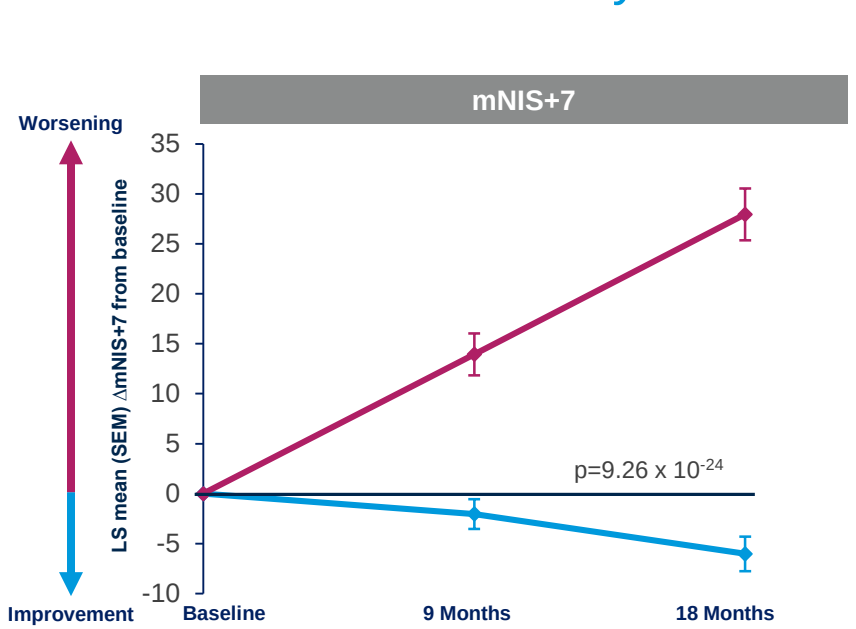
- **Alnylam sponsors no-charge third-party genetic testing and counseling for individuals who may carry gene mutations known to be associated with either hATTR amyloidosis, acute hepatic porphyrias, or primary hyperoxaluria type 1.**
- **All tests and services performed by independent third parties**
- **Genetic counselors provide information and support for people who have, or may be at risk for, genetic conditions**
  - Counseling available before, during or after genetic testing
- **Genetic testing service available in U.S. and Canada. Genetic counseling service available in U.S**

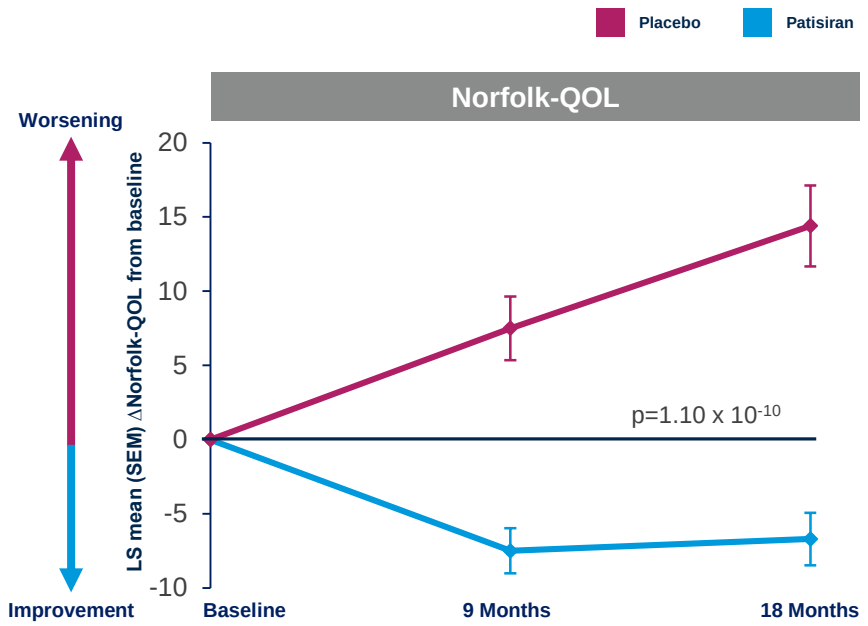
More information regarding this program available at:
www.alnylamact.com

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

Best-in-Class Product Profile

APOLLO Phase 3 Study Results





At 18 months

- -6.0 point change relative to baseline
- 34.0 point difference relative to placebo
- 56.1% of patients improved*

At 18 months

- -6.7 point change relative to baseline
- 21.1 point difference relative to placebo
- 51.4% of patients improved*

All secondary endpoints encompassing QOL, walk speed, activities of daily living, mBMI and autonomic dysfunction met

Best-in-Class Product Profile

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 5, 2018 VOL. 379 NO. 1

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

ABSTRACT

BACKGROUND

Patisiran, an investigational RNA interference therapeutic agent, specifically inhibits hepatic synthesis of transthyretin.

METHODS

In this phase 3 trial, we randomly assigned patients with hereditary transthyretin amyloidosis with polyneuropathy, in a 2:1 ratio, to receive intravenous patisiran (0.3 mg per kilogram of body weight) or placebo once every 3 weeks. The primary end point was the change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7; range, 0 to 304, with higher scores indicating more impairment) at 18 months. Other assessments included the Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) questionnaire (range, −4 to 136, with higher scores indicating worse quality of life), 10-m walk test (with gait speed measured in meters per second), and modified body-mass index (modified BMI, defined as [weight in kilograms divided by square of height in meters] × albumin level in grams per liter; lower values indicated worse nutritional status).

RESULTS

A total of 225 patients underwent randomization (148 to the patisiran group and 77 to the placebo group). The mean (±SD) mNIS+7 at baseline was 80.9±41.5 in the patisiran group and 74.6±37.0 in the placebo group; the least-squares mean (±SE) change from baseline was −6.0±1.7 versus 28.0±2.6 (difference, −34.0 points; P<0.001) at 18 months. The mean (±SE) baseline Norfolk QOL-DN score was 59.6±28.2 in the patisiran group and 55.5±24.3 in the placebo group; the least-squares mean (±SE) change from baseline was −6.7±1.8 versus 14.4±2.7 (difference, −21.1 points; P<0.001) at 18 months. Patisiran also showed an effect on gait speed and modified BMI. At 18 months, the least-squares mean change from baseline in gait speed was 0.08±0.02 m per second with patisiran versus −0.24±0.04 m per second with placebo (difference, 0.31 m per second; P<0.001), and the least-squares mean change from baseline in the modified BMI was −5.7±9.6 versus −119.4±14.5 (difference, 115.7; P<0.001). Approximately 20% of the patients who received patisiran and 10% of those who received placebo had mild or moderate infusion-related reactions; the overall incidence and types of adverse events were similar in the two groups.

CONCLUSIONS

In this trial, patisiran improved multiple clinical manifestations of hereditary transthyretin amyloidosis. (Funded by Alnylam Pharmaceuticals; APOLLO ClinicalTrials.gov number, NCT01960348.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Adams at the Department of Neurology, CHU Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre CEDEX, France, or at david.adams@aphp.fr.

N Engl J Med 2018;379:11-21.
DOI: 10.1056/NEJMoa1716153
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N ENGL J MED 379;1 NEJM.ORG JULY 5, 2018

11

Adams D, et al. *N Engl J Med*. 2018;379:11-21

* Improvement defined as patients with <0 point increase from baseline to 18 months

Alnylam Patient Access Philosophy

Objective: Make Therapies We Develop Available to Those Who Will Benefit from Them

Help Patients

- Above all, put patients first
- Partner with patient advocacy groups, healthcare providers, and payers to support disease awareness, diagnosis, and access efforts
- Actively listen and respond to all patients seeking support and provide meaningful, practical solutions

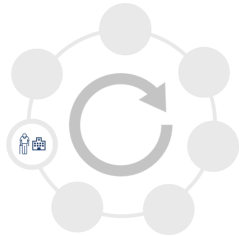
Deliver Value to Patients and Physicians

- Demonstrate evidence-based value objectively and transparently
- Establish responsible pricing that reflects value delivered to patients, caregivers and society
- Proactively pursue reimbursement through value-based agreements and other innovative approaches
- Commit to growth through continuous innovations, not arbitrary price increases

Be Proactive and Accountable

- Advocate for policies that promote innovation, value communication, and patient access
- Address and seek solutions to financial barriers to access
- Act with medical-scientific excellence and integrity
- Act with urgency to minimize the time it takes to get approved therapies to patients
- Track and report our efforts to help patients access therapy

Alnylam Assist™ is Here to Help Patients



Support and Solutions

Dedicated Case Manager

Alnylam Assist will connect patients with dedicated Alnylam Case Manager who can provide personalized support throughout treatment process.

Benefit Verification

Coverage for ONPATTRO™ will vary by plan and by patient. Alnylam Assist can help determine patient-specific coverage requirements.

Financial Assistance for Patients

Eligible patients may qualify for Alnylam Assist Quick Start Program, Patient Assistance Program (PAP), or Commercial Copay Program.

Treatment Coverage

Alnylam Assist can explain requirements and processes for prior authorizations, claims, and appeals.

Coding and Billing

A Field Reimbursement Director can provide education about billing, coding, and reimbursement process for ONPATTRO

Disease and Product Education

Patient Education Liaisons are available to help patients gain better understanding of disease.

Ordering Assistance

Alnylam Assist will help with ordering and facilitation of delivery via specialty distributor or specialty pharmacy.

Alnylam ASSIST™

8AM–7PM ET, Monday–Friday

1-833-256-2748 | 1-833-256-2747

To learn more about Alnylam Assist, visit www.AlnylamAssist.com.

Alnylam PHARMACEUTICALS

Patient Education Roles

Trained Disease State Experts that Provide Patient Education and Support

Engagement/Advocacy

Educate

Support and Solutions

- Provide ***customized education*** to patients
- Focused on ***patient education*** and ***motivating patients, families and caregivers to act***
- Roles with a background in ***Genetic Counseling*** or ***Nursing***

Center of Excellence Formation – German Example

Situational Analysis

- Underdeveloped, decentralized market
- 80% of patients undiagnosed or misdiagnosed
- Low disease awareness
- Poor referral network and treatment guidelines
- Few centers (i.e., APOLLO sites)

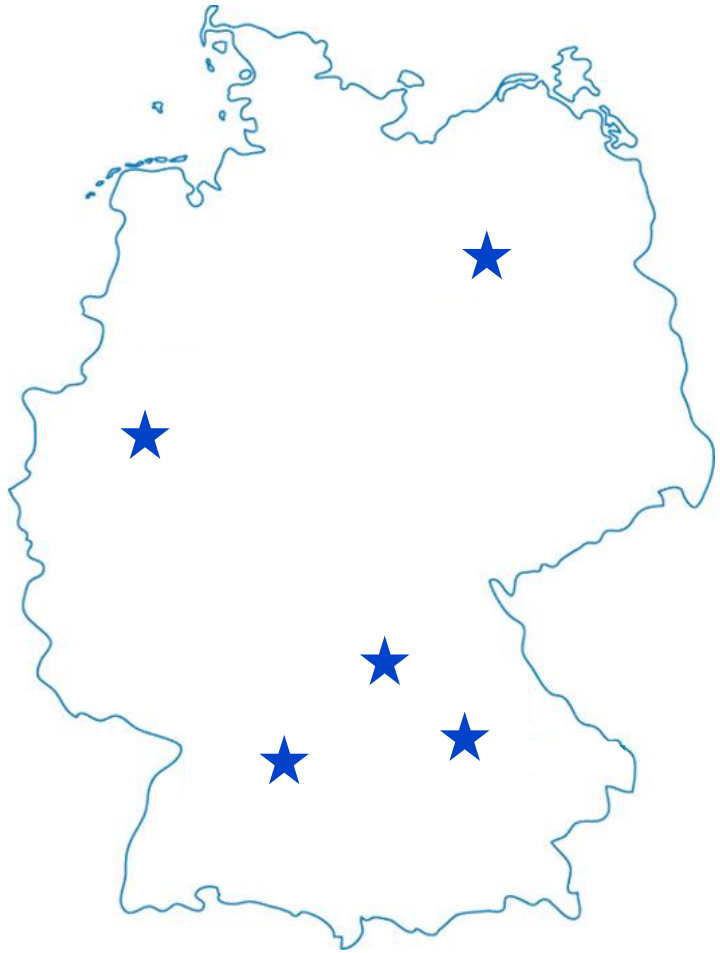
Opportunity

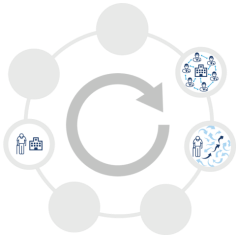
- University Hospital ideal example for emerging CoE:
  - Huge referral area in large region
  - Complete infrastructure for optimized patient care
  - Expert HCPs drive multidisciplinary collaboration (Neuro, Cardio, Nephro, Hem/Onc, Gastro)
  - Plan for establishment of a CoE for ATTR

Outcome

- Patient identification rate increased from <1 ATTR amyloidosis patient identified per month (pre-CoE formation) to >10 patients identified per month (post-CoE formation)

Centers of Excellence in Germany





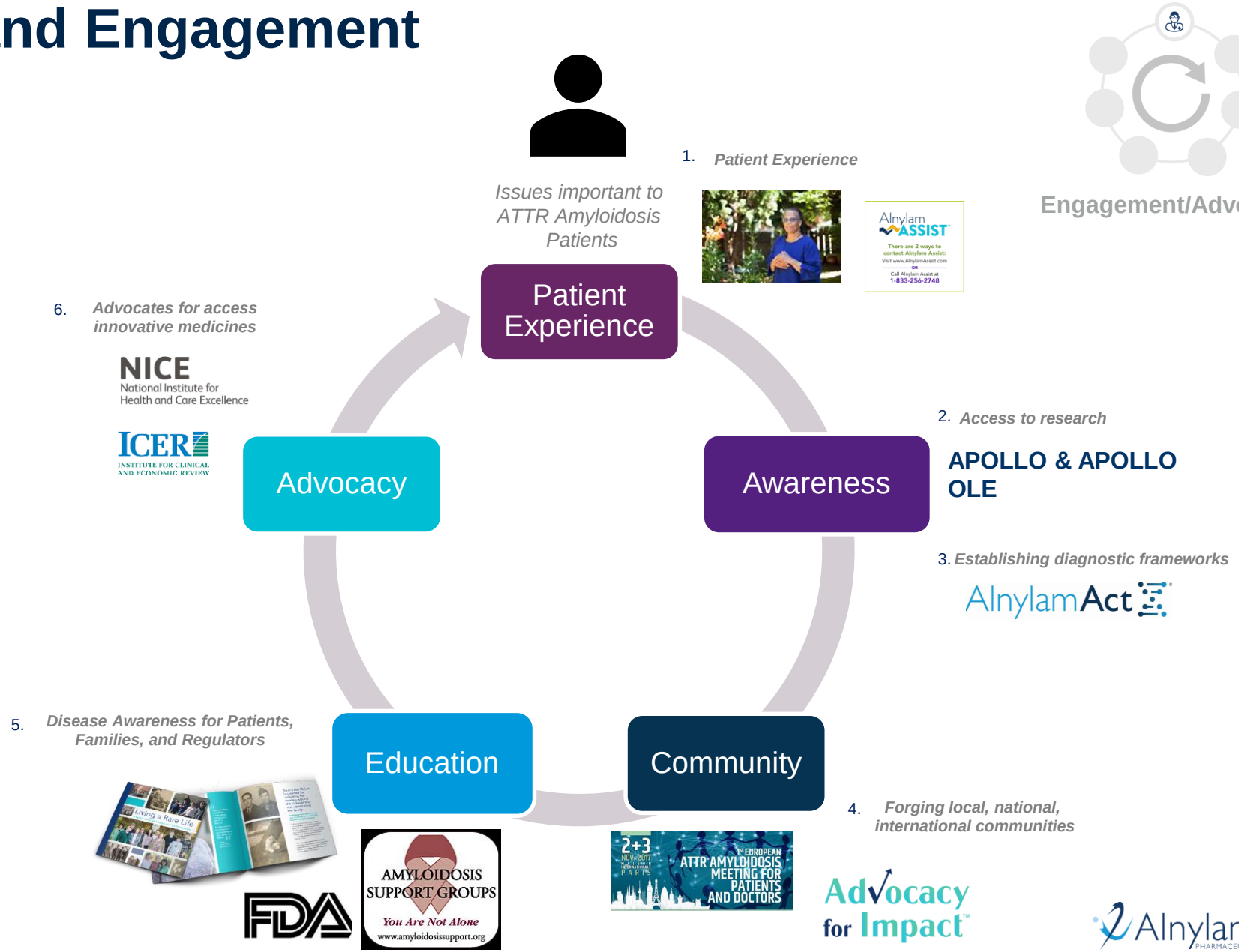
Educate

Diagnose/Expand

Support and Solutions

Patient Advocacy and Engagement

Alnylam's engagements with patients ***throughout drug development and approval process*** differentiate how we bring novel therapies to market and have ***real*** impact on patient lives

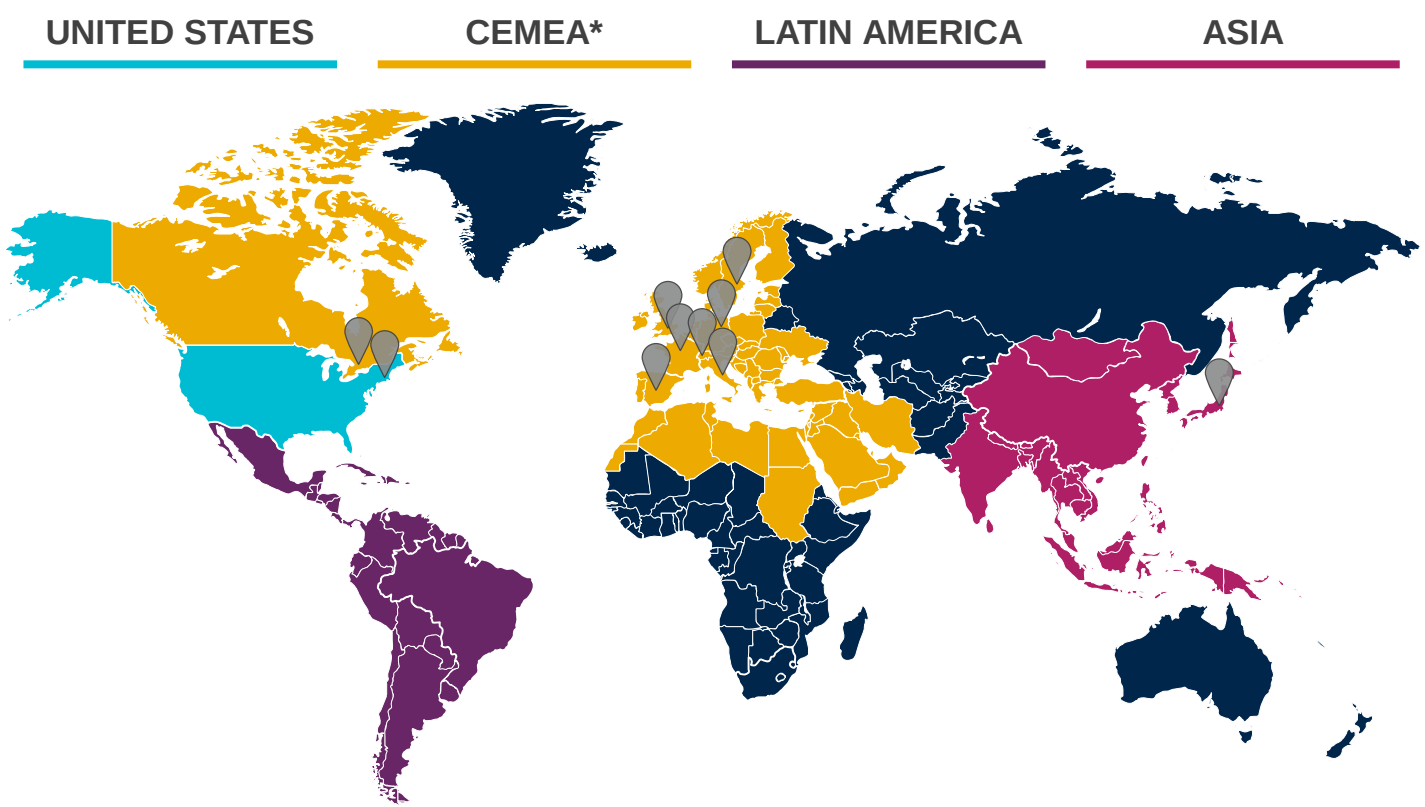


Global Commercialization Efforts Underway

EU and Asia in place
- EU launch underway (first market in Germany)
- Japan team on-board
- Preparing Canada and Switzerland
- Initiating Latin America, starting with Brazil

Regional Support
- Market Access
- Supply Chain

Country organizations built
- Country Manager
- Medical Affairs
- Sales and Marketing
- Local Market Access



* Canada, Europe, Middle East, North Africa

Commercial Innovation Summary

onpattro™ (patisiran) lipid complex injection

givosiran

lumasiran

vutrisiran

Alnylam PHARMACEUTICALS 2020

Multi-pronged strategy for commercialization

Reproducible approach for multiple rare disease drug launches

Facilitate global expansion by adapting for each geographic region

Achieve "Alnylam 2020" goals

Alnylam PHARMACEUTICALS

Alnylam R&D Day

Summary

Pioneering a whole new class of medicines and building a top biopharma

Executing on an R&D strategy that fuels future growth for years to come

Launching ONPATTRO, the first approved RNAi therapeutic, and building the leading ATTR amyloidosis franchise

Advancing late-stage pipeline with 5 Phase 3 programs - including givosiran and lumasiran - with 3 Phase 3 program readouts and 2 NDA filings in 2019 alone

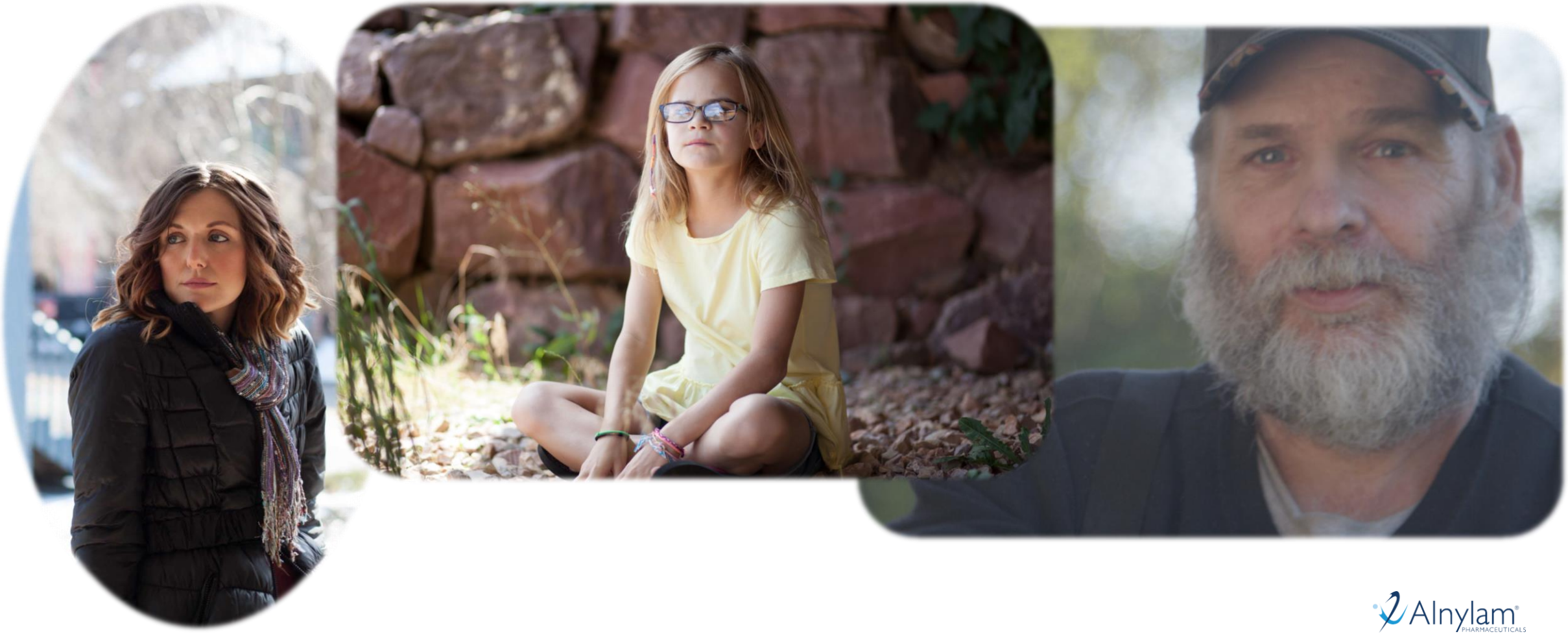
Leading RNAi therapeutics platform technologies for sustainable innovation

Fueling "Next Wave" programs for new high impact medicines for patients

Aiming to be as innovative as a commercial company as we've been as an R&D company

THANK YOU

To all the Patients, Investigators, HCPs, and our Alnylam Staff!



Alnylam PHARMACEUTICALS