Alnylam R&D Day

New York City

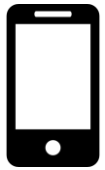
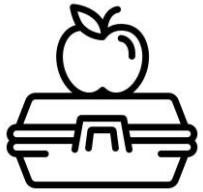
November 22, 2019

Alnylam® PHARMACEUTICALS

Agenda

Time	Topic
8:00 – 8:15 AM	**Building a Leading Biopharmaceutical Company**
8:15 – 9:00 AM	**R&D Engine for Pipeline Growth**
9:00 – 10:00 AM	**Transthyretin (TTR) Amyloidosis** • ONPATTRO Program Update • Cardiac Amyloidosis: A New Paradigm *Nitasha Sarswat, M.D., University of Chicago Medicine* • Expanding the ATTR Opportunity
10:00 – 10:30 AM	**GIVLAARI for Treatment of Acute Hepatic Porphyria**
10:30 – 10:50 AM	**Q&A Session 1**
10:50 – 11:05 AM	**Break**
11:05 – 11:25 AM	**Lumasiran, an Investigational Therapeutic for Primary Hyperoxaluria Type 1**
11:25 – 11:55 AM	**Next Wave of RNAi Opportunities**
11:55 AM – 12:10 PM	**Roadmap to Self-Sustainability**
12:10 – 12:30 PM	**Q&A Session 2**
12:30 – 12:35 PM	**Closing Statements**

Brief Reminders

- Please turn off or silence your cellphones 
- Breakfast available in Gershwin Foyer 
- Coffee to be available in Gershwin Foyer during break 
- Boxed lunch available in the Gershwin Foyer at meeting conclusion 
- Presentations available on Capella section of Alnylam website

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, including ONPATTRO® (patisiran) and GIVLAARI™ (givosiran); our progress in continuing to establish a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally, including ONPATTRO and GIVLAARI; our ability to successfully expand the indication for ONPATTRO in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, including our expected peak non-GAAP net operating losses in 2019, and to achieve a self-sustainable financial profile in the future; our ability to, obtain additional funding to support our business activities and establish and maintain business alliances; our dependence on third parties, including Regeneron, for development, manufacture and commercialization of certain products, including eye and CNS products, and Ironwood, for assistance with the education about and promotion of GIVLAARI; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent quarterly 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 references non-GAAP financial measures. 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 referenced 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.

Building a Leading Biopharmaceutical Company

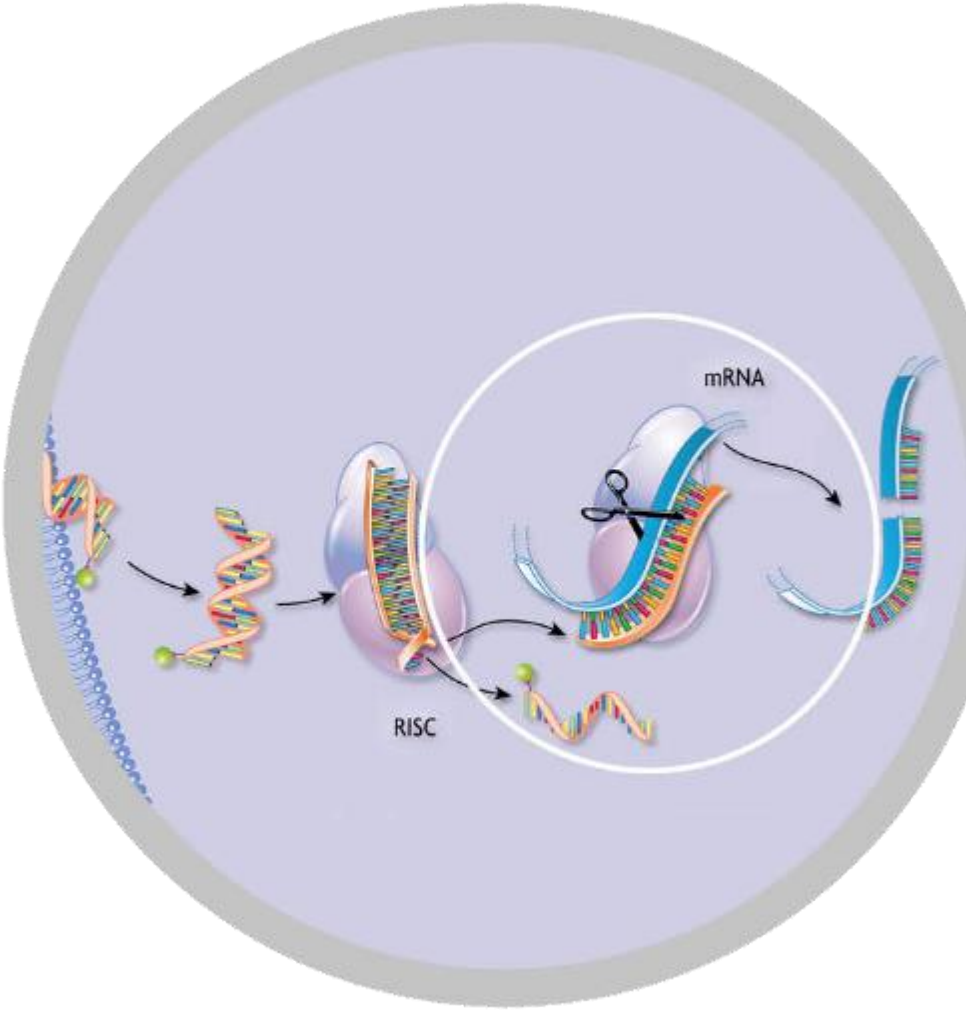
John Maraganore, Ph.D.
Chief Executive Officer

Alnylam® PHARMACEUTICALS

RNAi Therapeutics: New Class of Innovative Medicines

Clinically Proven Approach with Transformational Potential

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



Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	EARLY STAGE *(IND or CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 4)*	REGISTRATION/ COMMERCIAL[2]	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis*[3]	✓	●			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[4]	✓	●			●	Global
Patisiran	*ATTR Amyloidosis Label Expansion*	✓			●		Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*	✓			●		15-30% royalties
Inclisiran	*Hypercholesterolemia*	✓			●		Milestones & up to 20% royalties
Lumasiran	*Primary Hyperoxaluria Type 1*	✓	●		●		Global
Vutrisiran	*ATTR Amyloidosis*	✓			●		Global
Cemdisiran	*Complement-Mediated Diseases*	✓		●			50-50
Cemdisiran/Pozelimab Combo[5]	*Complement-Mediated Diseases*			●			Milestone/Royalty
ALN-AAT02	*Alpha-1 Liver Disease*	✓		●			Global
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*	✓		●			50-50 option rights post-Phase 2
ALN-AGT	*Hypertension*			●			Global

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

[2] Includes marketing application submissions

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

[4] Approved in the U.S. for the treatment of adults with acute hepatic porphyria

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

As of November 2019

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ALN-AGT	*Hypertension*			●			Global

- 2 Marketed Products
- 10 Clinical Programs
- 6 Late Stage Programs
- 3 Breakthrough Designations
- Substantial Global Rights

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As of November 2019

The first RNAi therapeutic is

APPROVED IN U.S., EU, CANADA & JAPAN

onpattro®

(patisiran) lipid complex injection 10 mg/5 mL

onpattro®

2 mg/mL concentrate for solution for infusion patisiran

オンパットロ®

パチシランナトリウム注射液2mg/mL

NOW APPROVED

in the U.S.

GIVLAARI™

(givosiran) injection for subcutaneous use
189 mg/mL

Two Horizons for Alnylam

Next 1-2 Years

- Creating a Global Commercial Company

Next 3-6 Years

- Building a Top-Tier Biotech

Alnylam 2020 Goals

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

		2020*		
		Early	Mid	Late
onpattro® (patisiran) lipid complex injection (ATTR Amyloidosis)	Global Commercial Execution	●	●	●
	Brazil Approval		●	
	Additional Country Launches	●	●	●
	Complete APOLLO-B Enrollment			●
GIVLAARI™ (givosiran) injection for subcutaneous use 189 mg/mL (Acute Hepatic Porphyria)	EMA Approval	●		
	Global Commercial Execution	●	●	●
	Additional ENVISION Results		●	
	Additional Country Filings and Approvals	●	●	●
VUTRISIRAN (ATTR Amyloidosis)	Complete HELIOS-A Enrollment	●		
	HELIOS-B Enrollment	●	●	●
LUMASIRAN (Primary Hyperoxaluria Type 1)	File NDA/MAA	●		
	FDA/EMA Approval			●
	ILLUMINATE-B Phase 3 Topline		●	
ADDITIONAL CLINICAL PROGRAMS	Continue to advance early/mid-stage pipeline; File 3 new INDs; Present clinical data	●	●	●
PARTNERED PROGRAMS				
INCLISIRAN (Hypercholesterolemia)	FDA Approval			●
	MAA Filing	●		
	ORION-4 CVOT Phase 3 Enrollment	●	●	●
FITUSIRAN (Hemophilia and RBD)	Support Sanofi on ATLAS Phase 3	●	●	●

Alnylam 2020 Goals

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

		2020*		
		Early	Mid	Late
onpattro (patisiran) lipid complex injection	Global Commercial Execution	●	●	●
	Brazil Approval		●	
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G (gi				
(Acu			●	●
				●
(A			●	●
(Prima				●
			●	
ADI			●	●
INCLISIRAN (Hypercholesterolemia)	FDA Approval			●
	MAA Filing	●		
	ORION-4 CVOT Phase 3 Enrollment	●	●	●
FITUSIRAN (Hemophilia and RBD)	Support Sanofi on ATLAS Phase 3	●	●	●

- Continued Global ONPATTRO Commercialization
- Global GIVLAARI Launch
- 1 NDA Filing
- 2 Approvals
- 6 Phase 3/4 Programs Ongoing
- 1 Phase 3 Study Readout

Multiple Launches Planned in Next 12-24 Months

2018	2019	2020-2021		Partnered programs*: 2020-2021	
onpattro® (patisiran) lipid complex injection 10 mg/5 mL	GIVLAARI™ (givosiran) injection for subcutaneous use 189 mg/mL	**Lumasiran**	**Vutrisiran**	**Fitusiran**	**Inclisiran**
ONPATTRO is indicated in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults^	GIVLAARI is indicated in the U.S. for the treatment of adults with acute hepatic porphyria†	Primary hyperoxaluria type 1	ATTR amyloidosis	Hemophilia	Hypercholesterolemia

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

* Sanofi Genzyme is leading and funding development of fitusiran and will commercialize fitusiran, if successful;
The Medicines Company is leading and funding development of inclisiran and will commercialize Inclisiran, assuming regulatory approvals

^ ONPATTRO is approved in Canada for the polyneuropathy of hATTR amyloidosis in adults, the EU for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, and Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; For additional information on ONPATTRO, see Full Prescribing Information

† Alnylam has filed for marketing authorization for givosiran in Europe and Brazil and plans to file in Japan and other countries in 2020; For additional information on GIVLAARI, see Full Prescribing Information

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


Alnylam®
PHARMACEUTICALS
2020
3 STArs 4
3 Marketed Products 4
10 Clinical Programs 14
4 Late Stage Programs 6

Two Horizons for Alnylam

Next 1-2 Years

- Creating a Global Commercial Company

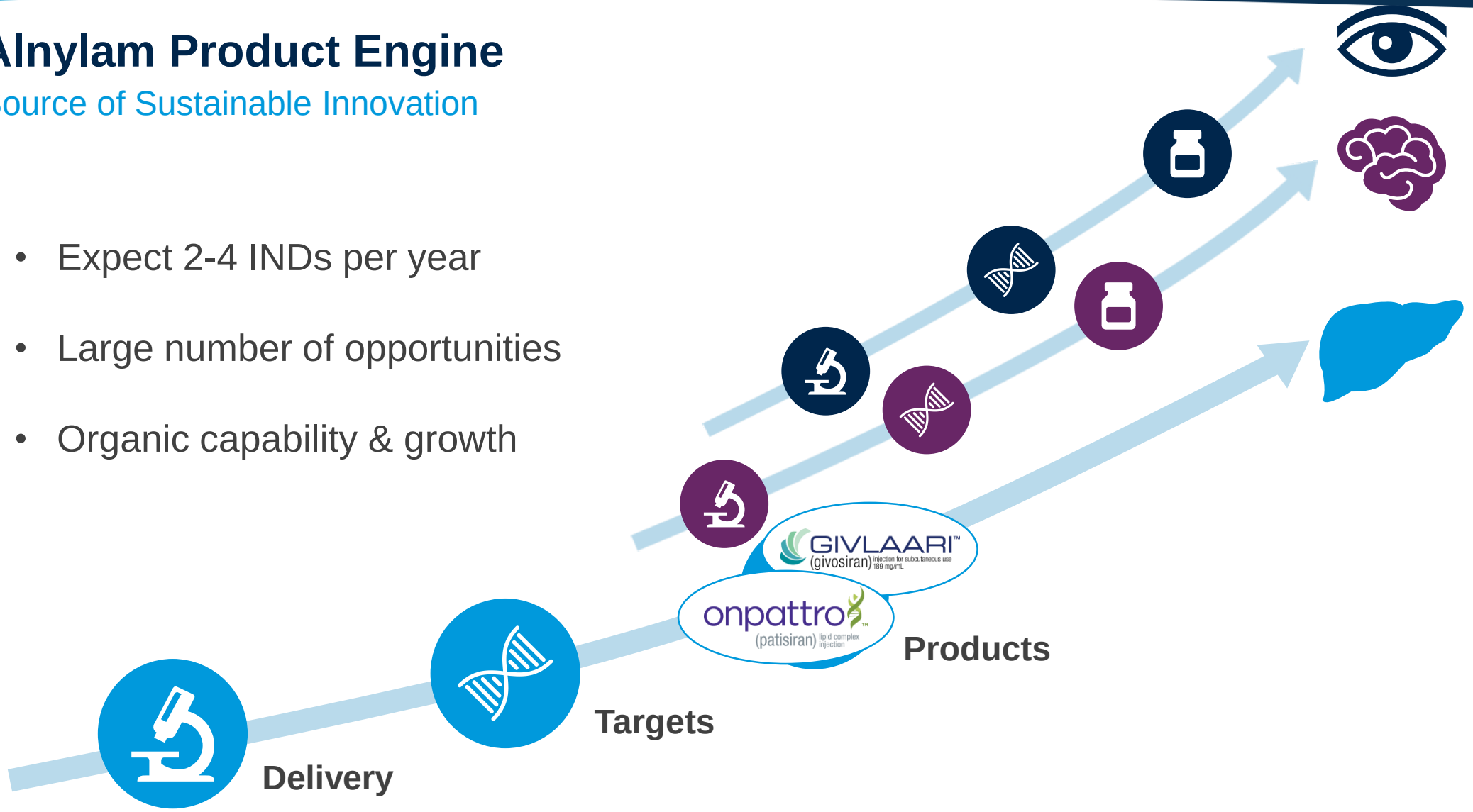
Next 3-6 Years

- Building a Top-Tier Biotech

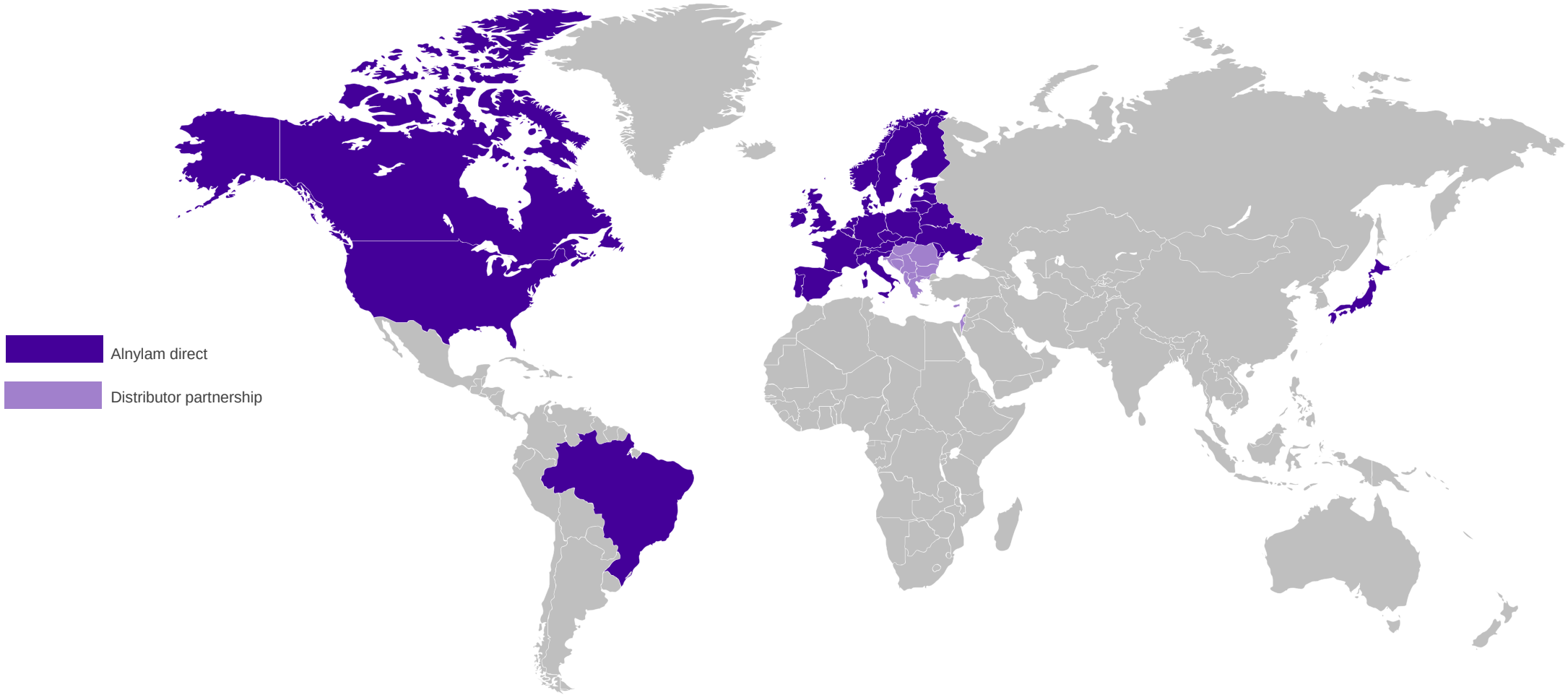
Alnylam Product Engine

Source of Sustainable Innovation

- Expect 2-4 INDs per year
- Large number of opportunities
- Organic capability & growth



Global Commercial Footprint



- ONPATTRO available through direct distribution in 11 countries
- ONPATTRO available in 14 additional countries through third party distributors

Path to Self-Sustainability

Becoming a profitable, self-sustainable company is a top Alnylam priority

Focused on key levers affecting pathway to profitability

- Topline growth
- Disciplined investment

The path to financial self-sustainability begins now

- We project 2019 will be our peak non-GAAP net operating loss year

Building a Top-Tier Biotech

Potential for Significant Transformation of Alnylam over Next 6 Years

2019

2	Approved Products
6	Late Stage Programs
4	STArs
	10+ Markets
~1K	Employees
	CMOs

2025

8+	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 New Class of Medicines

Significant Opportunity to Transform Human Health

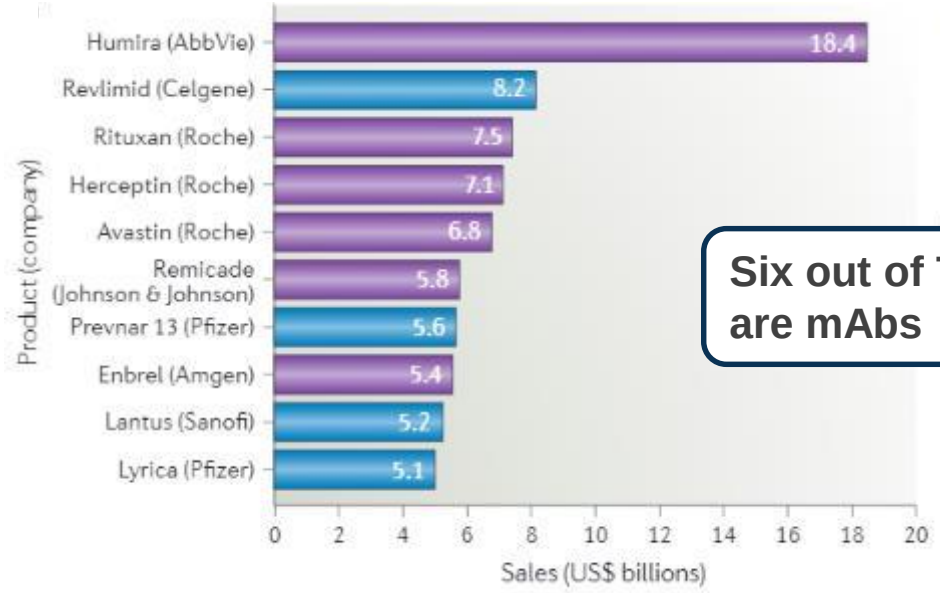
mAb Therapeutics

Discovery by Kohler & Milstein *Nature* 256: 495	Nobel Prize in Physiology or Medicine to Jerne, Kohler & Milstein	ReoPro – first mAb 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 to market
1998 →	**2006** →	**2018**
	8 years	*12 years*

Top selling drugs in 2018*



Six out of Top Ten are mAbs

Nature Reviews Drug Discovery, 17. 232 (2018)

AT OUR CORE… PATIENTS

Why We Do What We Do!

Mayah, living with PH1 (USA)

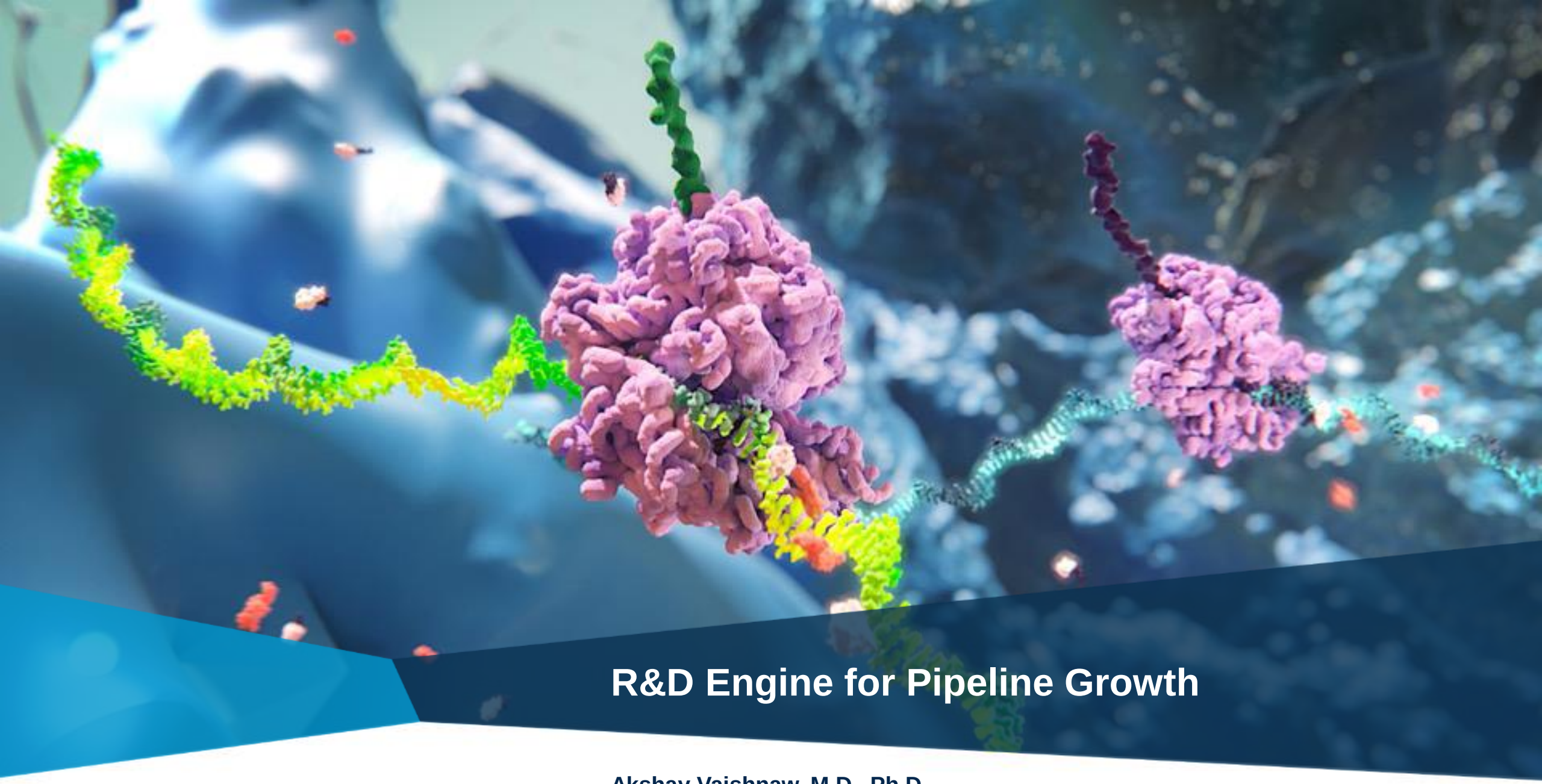
Veronika, living with porphyria (Spain)

David, living with hATTR amyloidosis (Canada)

The Skinner Family, three of four children living with PH1 (USA)

Colin, living with porphyria (USA)

CeCe, Living with hATTR amyloidosis (USA)



R&D Engine for Pipeline Growth

Akshay Vaishnaw, M.D., Ph.D.
President, Research & Development

Alnylam® PHARMACEUTICALS

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- Product engine for sustainable pipeline
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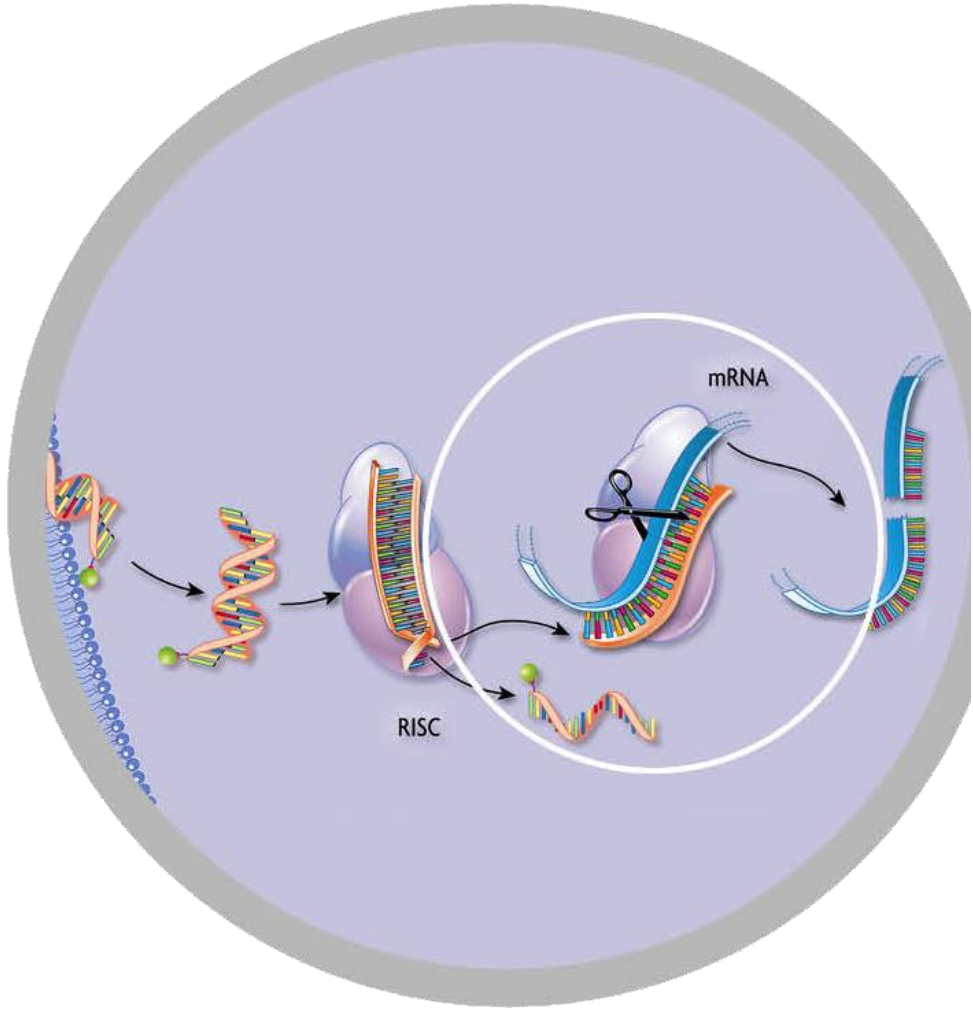
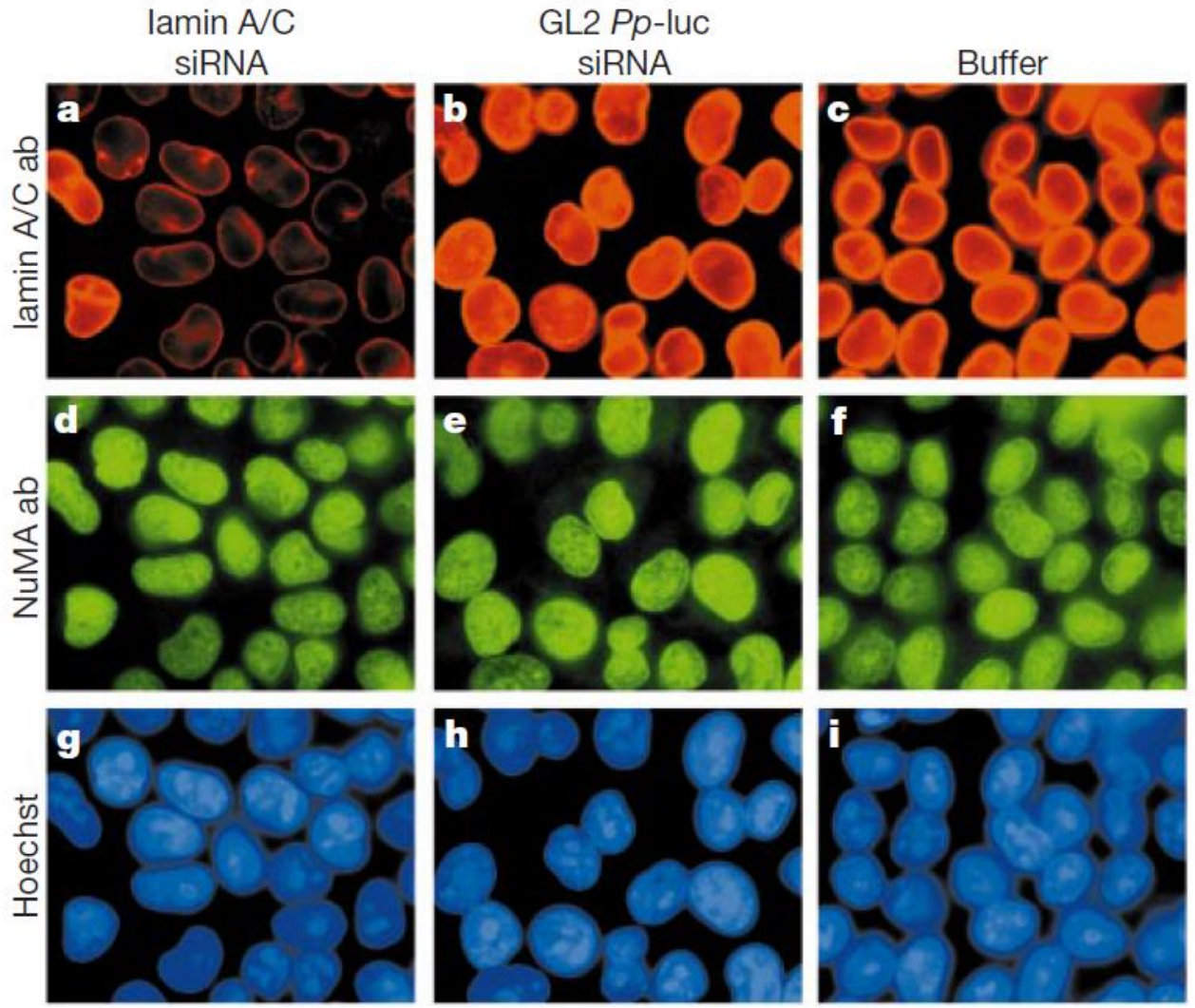


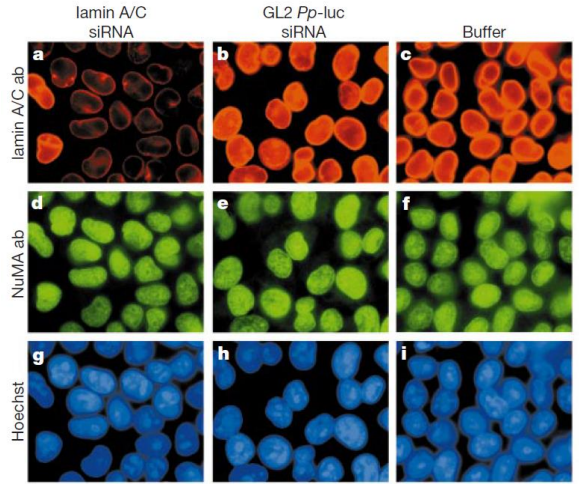
In Vitro Data that Started Alnylam

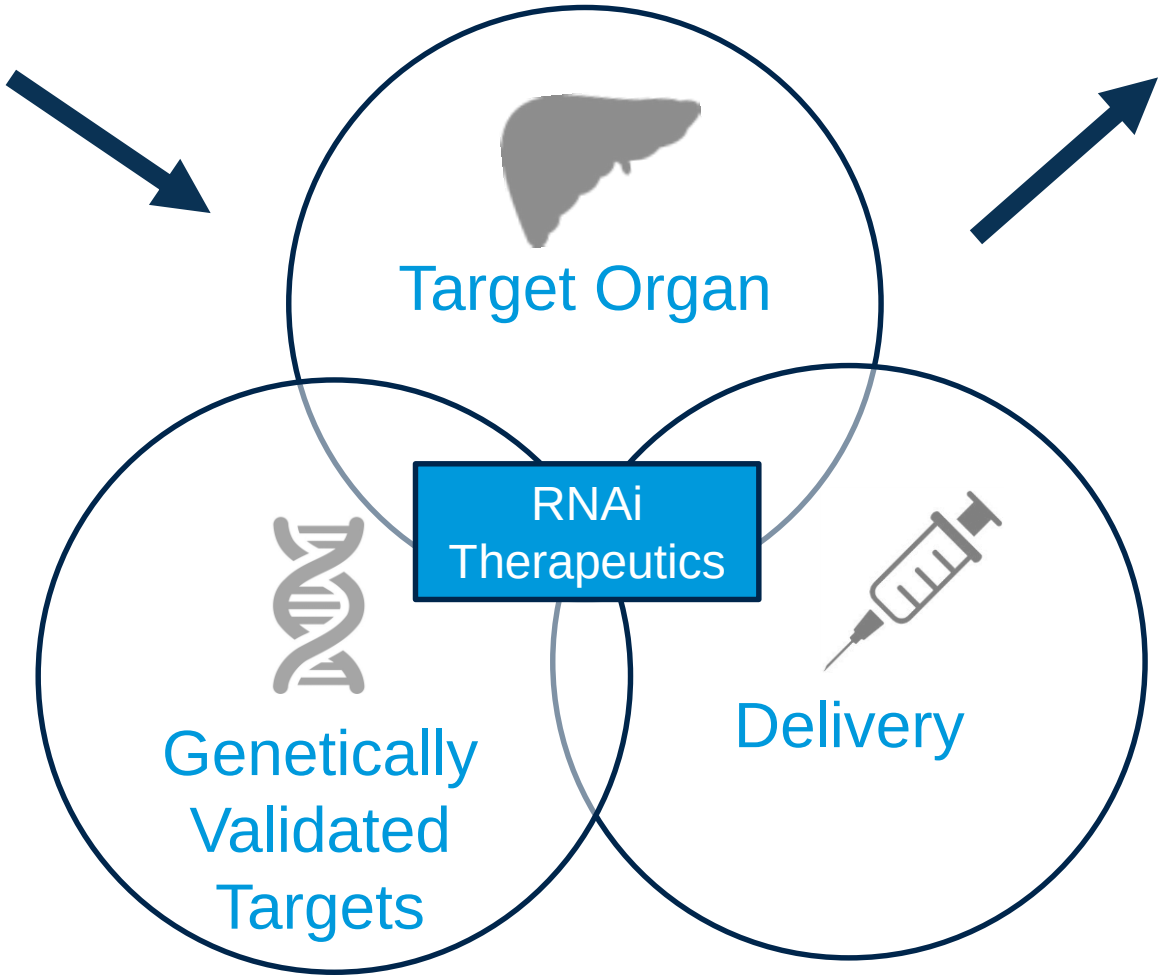
Elbashir et al., Nature, 2001;411:494-98



Focused R&D Strategy

Turning an *In Vitro* Observation into a New Class of Medicines





Agenda

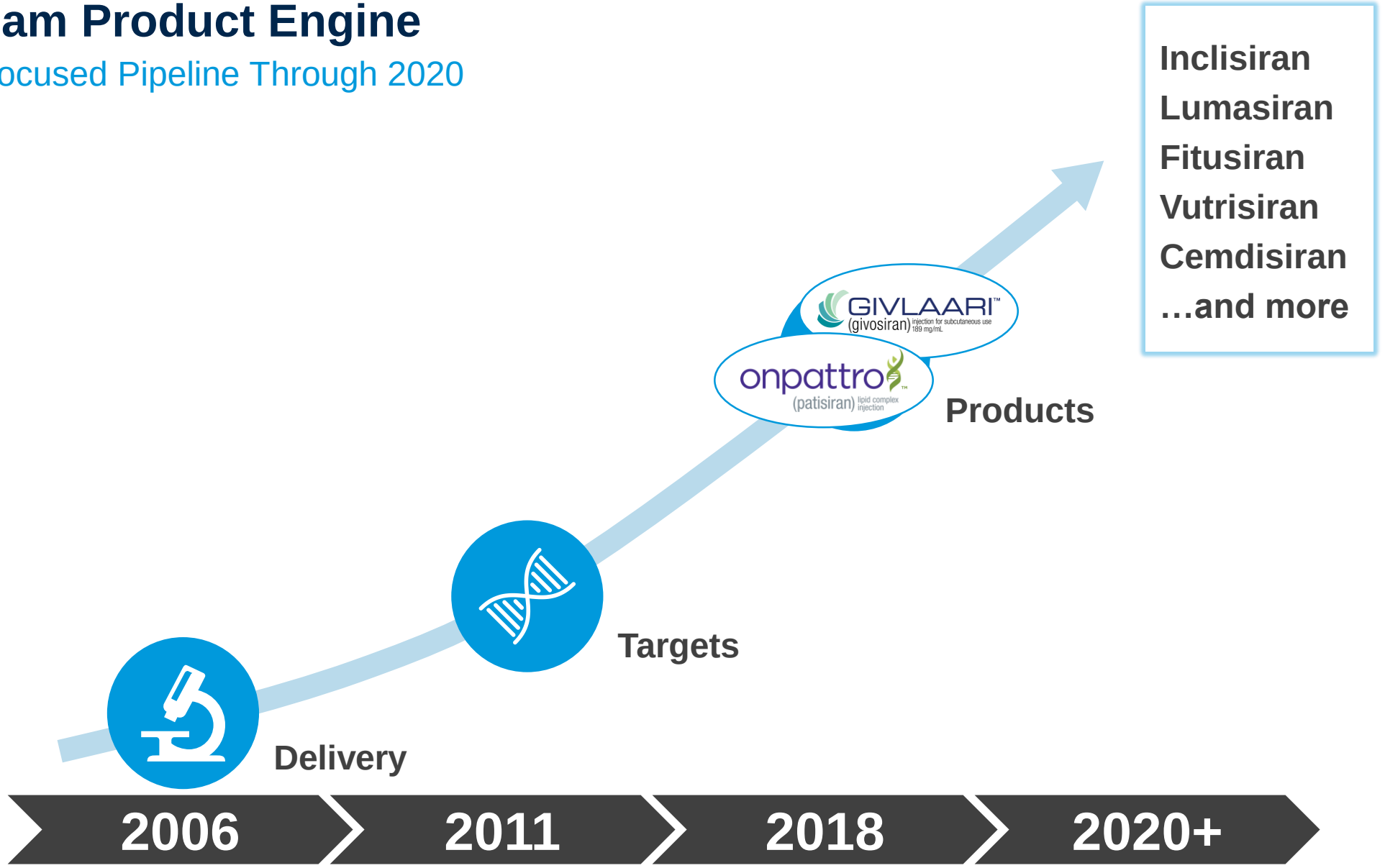
Progress to Date

Evolving the Pipeline

Future Outlook

Alnylam Product Engine

Liver-Focused Pipeline Through 2020



* Inclisiran, lumasiran, fitusiran, vutrisiran and cemdisiran are investigational RNAi therapeutics. Their respective safety and efficacy have not been evaluated by the U.S. FDA or any other health agency

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As of November 2019

Fitusiran ATLAS Phase 3 Program

Hemophilia A and B

ATLAS-INH

- Adults and adolescents with hemophilia A or B with inhibitors
- Currently manage bleeds with on-demand bypassing agent therapy
- N~50

2:1 RANDOMIZATION

- 9 months fitusiran
- OR
- 9 months on-demand BPA

Primary Endpoints:
- ABR†

Secondary Endpoints:
- Spontaneous ABR
- Joint ABR
- QOL (Haem-A-QOL)

ATLAS-A/B

- Adults and adolescents with hemophilia A or B without inhibitors
- Currently manage bleeds with on-demand (OD) factor replacement therapy
- N~100

2:1 RANDOMIZATION

- 9 months fitusiran
- OR
- 9 months on-demand factor

Primary Endpoints:
- ABR‡

Secondary Endpoints:
- Spontaneous ABR
- Joint ABR
- QOL (Haem-A-QOL)

ATLAS-PPX

- Adults and adolescents with hemophilia A or B with or without inhibitors
- Currently manage bleeds prophylactically
- N~100

6 months PPX factor/BPA → 7 months fitusiran

Primary Endpoints:
- ABR in factor/BPA and fitusiran period

Secondary Endpoints:
- Spontaneous ABR
- Joint ABR
- QOL (Haem-A-QOL)

Patients who complete the study may be eligible for fitusiran treatment in ATLAS-OLE study

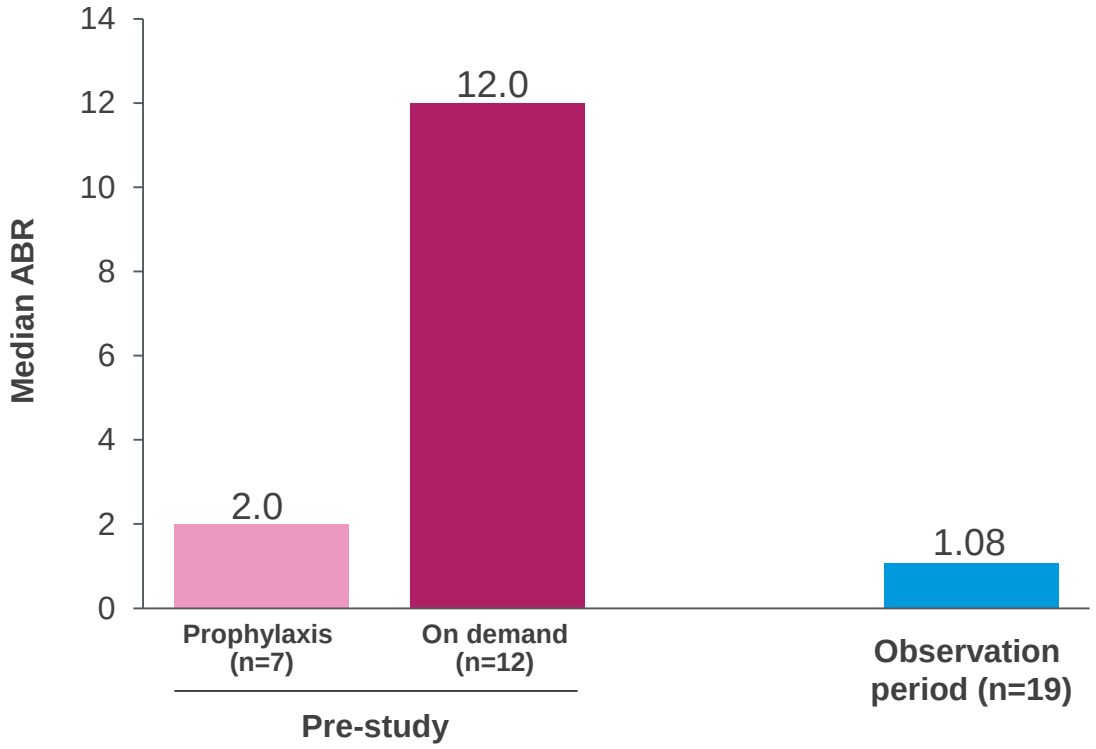
† ATLAS-INH powered to detect as little as a 60% reduction from control to fitusiran
‡ ATLAS-A/B powered to detect as little as a 50% reduction from control to fitusiran

Fitusiran Phase 2 OLE Interim Results

Exploratory Analysis of Bleeding Events

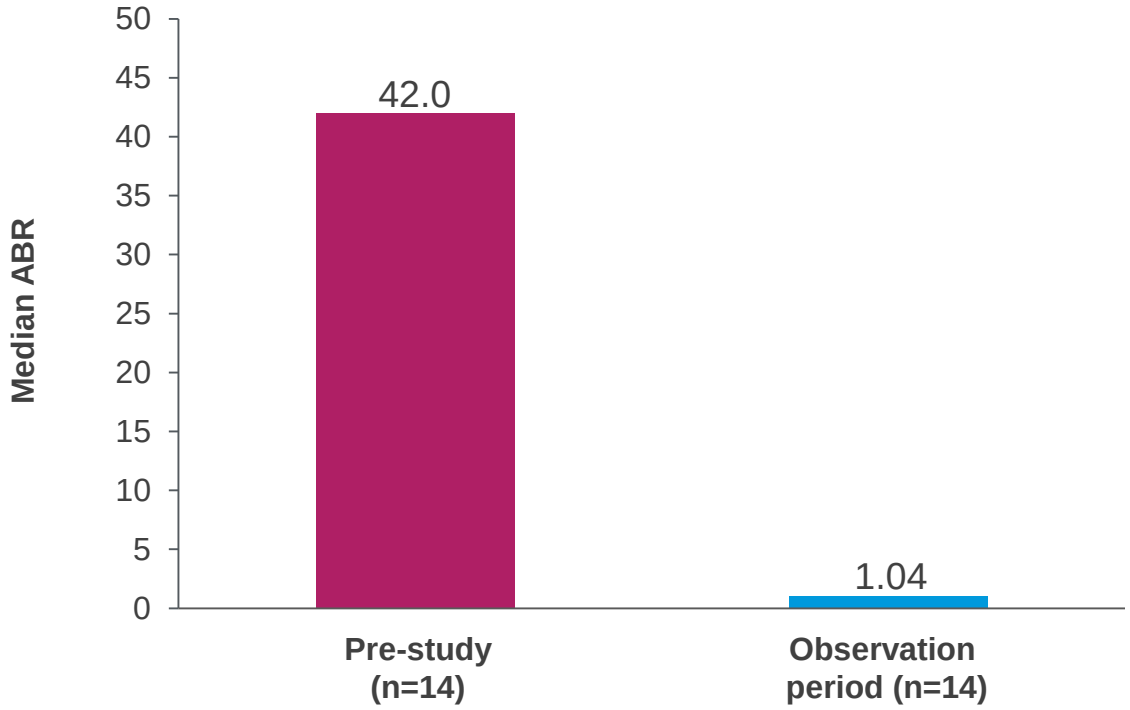
Overall median ABR of 1.08

ABR in subjects without inhibitors



Median duration in observation period:
25 months (range: 5–33 months)

ABR in subjects with inhibitors



Median duration in observation period:
18 months (range: 7–25 months)

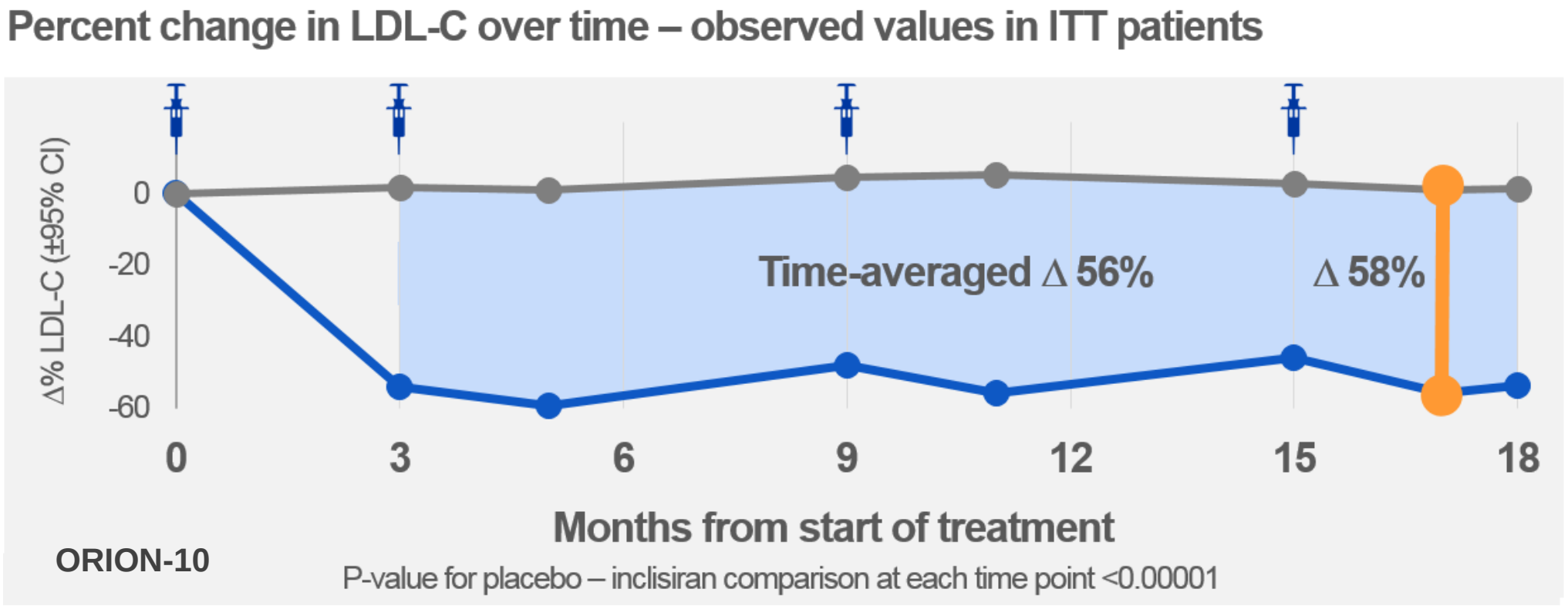
Pasi et al., ISTH 2019

Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Data transfer: May 2, 2019. ABR and duration represent pooled data from Phase 1 and Phase 2 OLE studies. Phase 1 data are included if gap between studies was ≤56 days. Only subjects with 28 days of follow-up during the observation period are included in this analysis.

Inclisiran ORION-10+11 Results

Durable, Potent, and Consistent LDL-C Lowering Over 18 Months



- Inclisiran safety profile similar to placebo, with no adverse changes in laboratory markers
- Injection site events 2.6-4.7% - predominantly mild and none persistent
- ORION-10+11: Numerically fewer CV events reported for inclisiran than placebo (exploratory endpoint)

NDA submission expected **Q4 2019**

MAA submission expected **Q1 2020**

Wright et al., AHA 2019; Ray et al., ESC Congress 2019
All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

ORION-10+11 Pooled Data: Safety and Tolerability of Inclisiran

No Evidence of Liver, Kidney, Muscle or Platelet Toxicity

Laboratory tests Safety population[1]		Placebo N = 1,582		Inclisiran N = 1,592	
Liver function	ALT >3x ULN	6	(0.38%)	6	(0.38%)
	AST >3x ULN	9	(0.57%)	6	(0.38%)
	ALP >2x ULN	5	(0.32%)	6	(0.38%)
	Bilirubin >2x ULN[2]	11	(0.70%)	10	(0.63%)
Kidney function	Creatinine >2 mg/dL	41	(2.59%)	35	(2.20%)
Muscle	CK >5x ULN	17	(1.07%)	20	(1.26%)
Hematology	Platelet count <75x10^9/L	1	(0.06%)	1	(0.06%)

[1] Safety population includes all patients who received at least 1 dose of study medication and individual patients may be counted in more than one category

[2] No cases met Hy's Law

Growing Safety Database Supports Expansion to Large Indications

Genetic Medicines

ONPATTRO® (patisiran)
GIVLAARI™ (givosiran)
Inclisiran
Lumasiran
Fitusiran
Vutrisiran
Cemdisiran

Hepatic Infectious Diseases, CV/Metabolic and CNS/Ocular Disorders

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

Agenda

Progress to Date

Evolving the Pipeline

Future Outlook

Evolving the Pipeline

Strategic Priorities

Building the Pipeline

Optimizing Safety Profile

Advancing Larger Market Opportunities

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	EARLY STAGE *(IND or CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 4)*	REGISTRATION/ COMMERCIAL[2]	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis*[3]	✓	✓			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[4]	✓	✓			●	Global
Patisiran	*ATTR Amyloidosis Label Expansion*	✓			●		Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*	✓			●		15-30% royalties
Inclisiran	*Hypercholesterolemia*	✓			●		Milestones & up to 20% royalties
Lumasiran	*Primary Hyperoxaluria Type 1*	✓	✓		●		Global
Vutrisiran	*ATTR Amyloidosis*	✓			●		Global
Cemdisiran	*Complement-Mediated Diseases*	✓		●			50-50
Cemdisiran/Pozelimab Combo[5]	*Complement-Mediated Diseases*			●			Milestone/Royalty
ALN-AAT02	*Alpha-1 Liver Disease*	✓		●			Global
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*	✓		●			50-50 option rights post-Phase 2
ALN-AGT	*Hypertension*			●			Global

[1] POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2] Includes marketing application submissions
[3] Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy
[4] Approved in the U.S. for the treatment of adults with acute hepatic porphyria
[5] Cemdisiran is currently in Phase 2 development and pozelimab is currently in Phase 1 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics
As of November 2019

Building the Pipeline

Cemdisiran Phase 1/2 (Part A, SAD) Results*

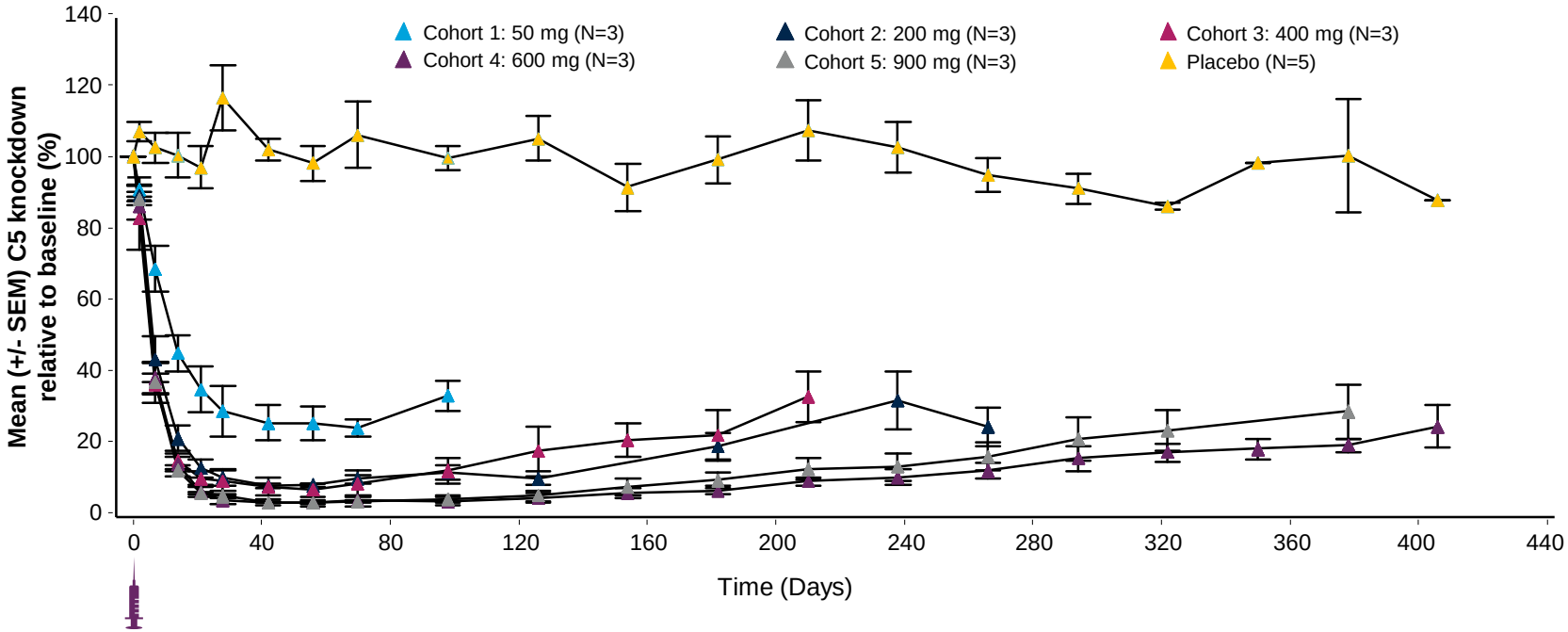
Serum C5 knockdown following single dose of cemdisiran in healthy volunteers

Maximum C5 knockdown relative to baseline up to 99%

Mean maximum (± SEM) C5 knockdown: 98 ± 0.9% (600mg)

Mean (± SEM) C5 knockdown:

- Day 98 (600 mg): 97 ± 1.1%; Day 406 (600 mg): 76 ± 6.0%



SAD: Single ascending dose

* Data as of 13 October 2016

IgA Nephropathy

Background

Epidemiology

- Commonest cause of glomerulonephritis worldwide

Pathophysiology

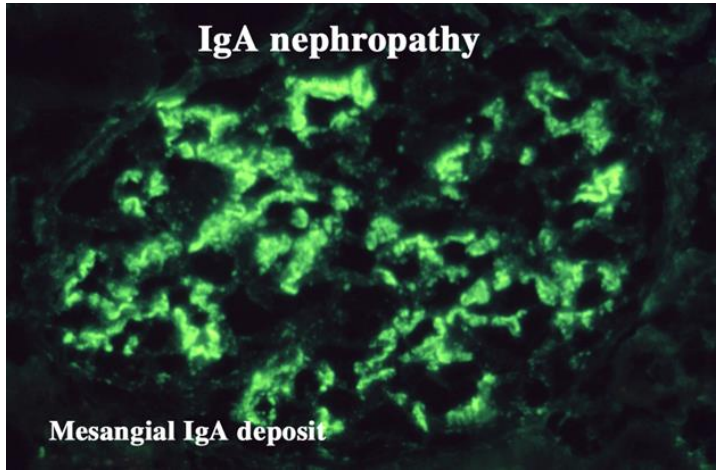
- ~6% have family history of disease
- Abnormally galactosylated IgA1 is antigenic leading to autoantibody formation, glomerular immune complex deposition and complement activation (C3, C5, MAC) causing inflammation

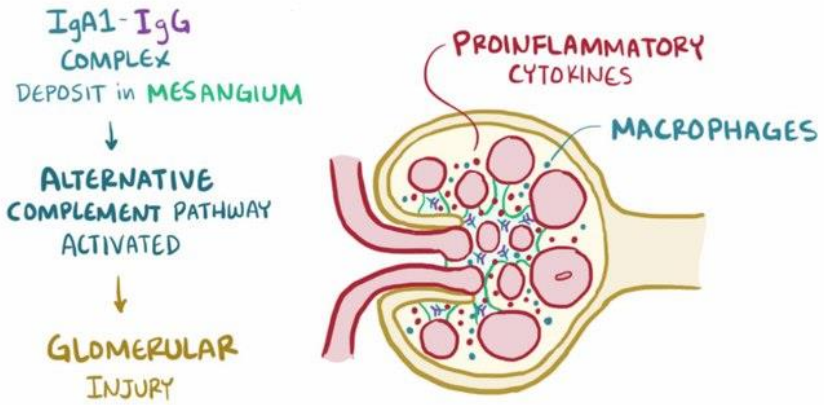
Clinical Features

- Often presents after respiratory or GI infection with hematuria and variable degree of proteinuria
- Symptoms can be recurrent
- 30-40% can evolve to chronic renal failure
- Rarely presents with rapid deterioration to end-stage renal disease

Unmet Need

- Only definitive therapy is renal transplantation, but disease can recur in graft





Cemdisiran Phase 2 Study

Randomized, Double-Blind Study in Patients with IgA Nephropathy

N ~ 30
Patient Population

- Biopsy proven diagnosis of IgA nephropathy
  - 18 years and older
- 24hr urine protein >1,000 mg/d & hematuria >10 RBC/hfp
- EGFR >30 ml/min
- On stable, optimized treatment with ACE/ARBs ≥3 months

2:1 RANDOMIZATION

Cemdisiran
SC q4w
600 mg

or

Placebo
SC q4w

Primary Endpoint

- Change in proteinuria at 50 weeks

Key Secondary Endpoints

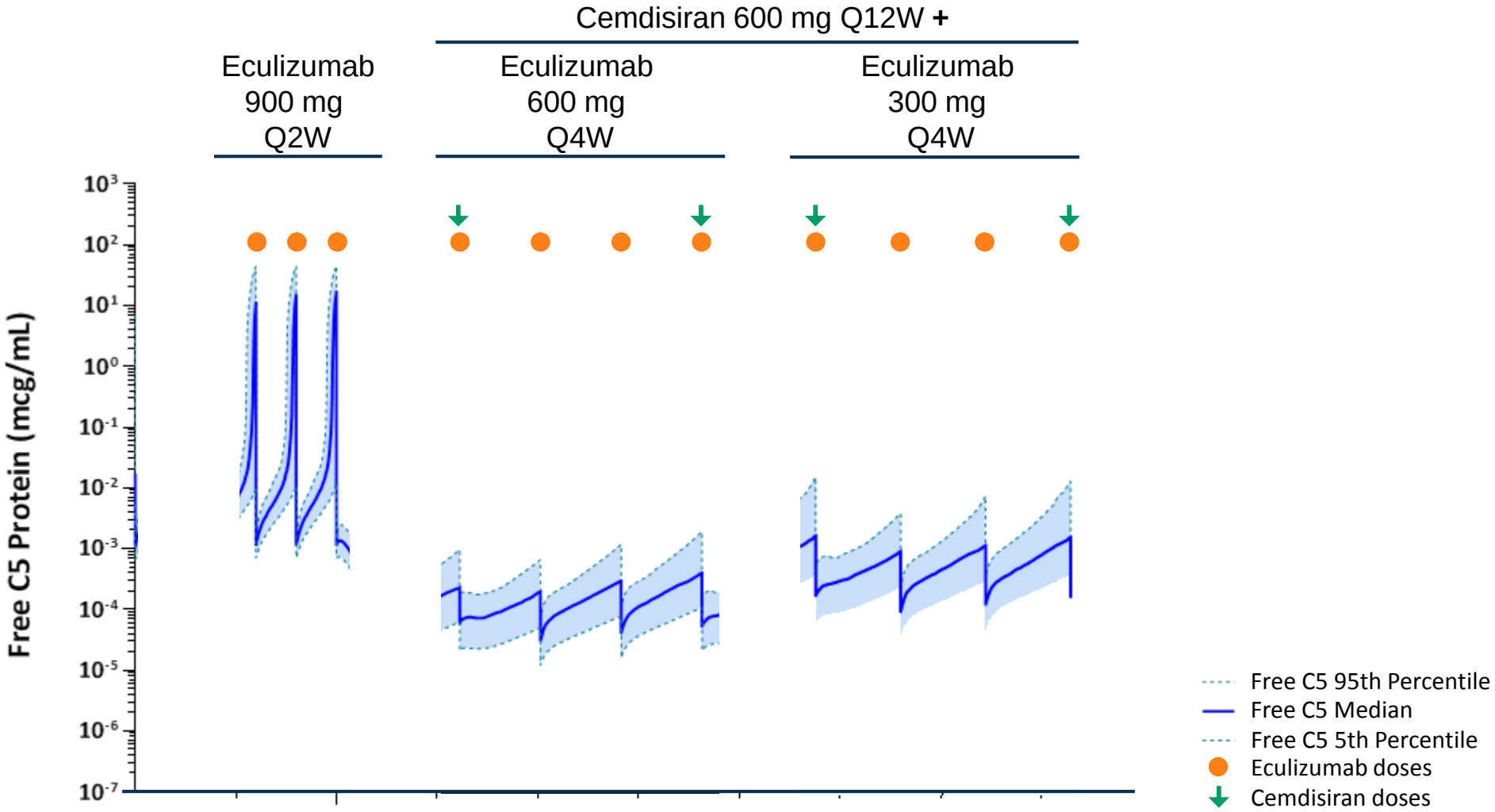
- % of patients with full clinical remission (UP <0.3 gm/24h)
- % of patients with partial clinical remission (UP <1 gm/24h)
- Change in EGFR
- Complement Activity

52-Week Treatment Extension

Initial data expected **2021**

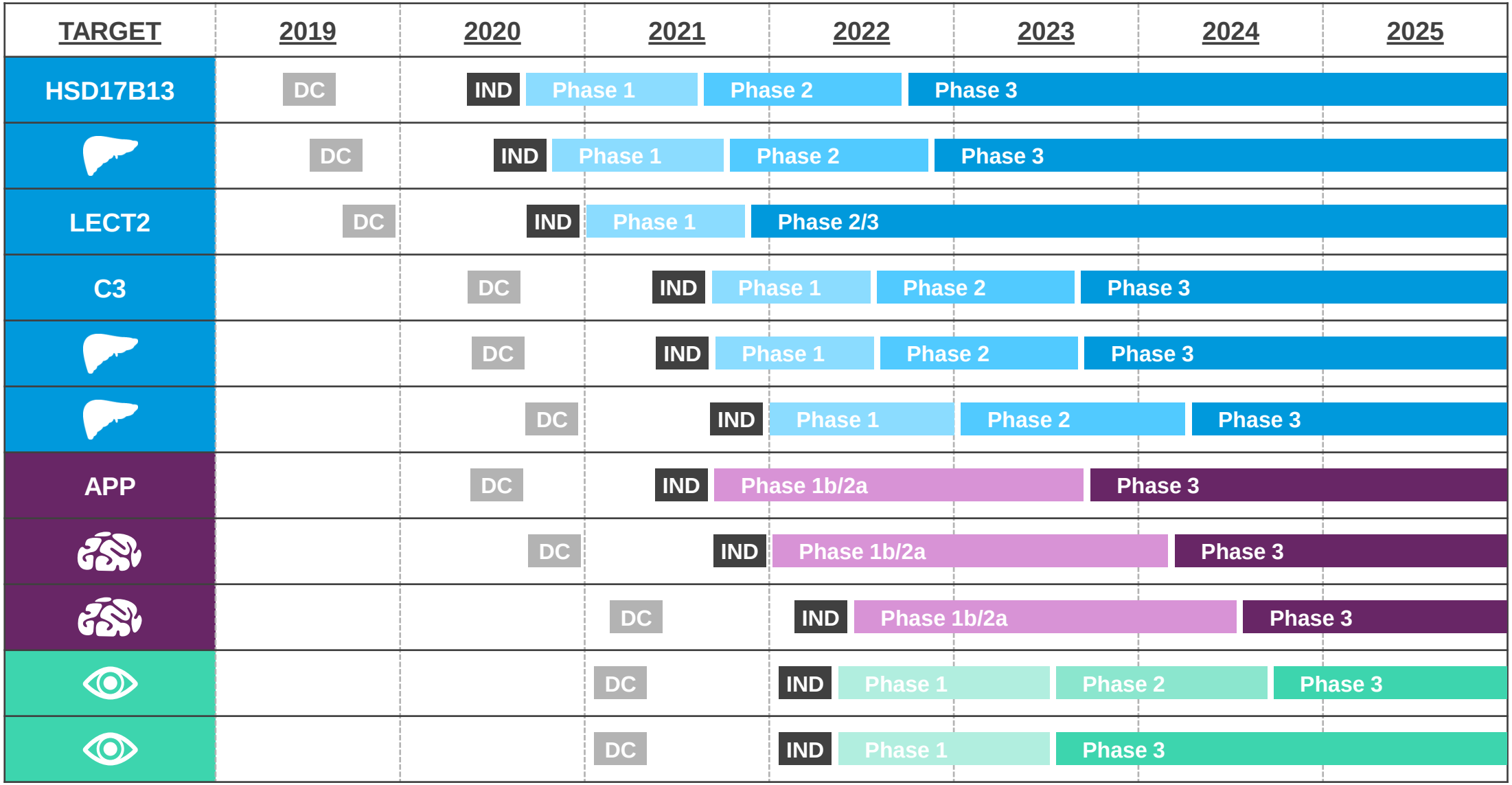
Quarterly Cemdisiran May Enable Monthly, SC Anti-C5 Mab

Results of PK/PD Modeling with Eculizumab



* 100 subjects were simulated to obtain 95th percentiles. Figure depicts three independent simulations and does not represent actual clinical results.
X-axis tick marks indicate Q4W intervals.

Illustrative Flow of Potential Next Wave INDs (2020-2022)



Note: Timing and length of clinical studies are estimates for illustrative purposes

Evolving the Pipeline

Strategic Priorities

Building the Pipeline

Optimizing Safety Profile

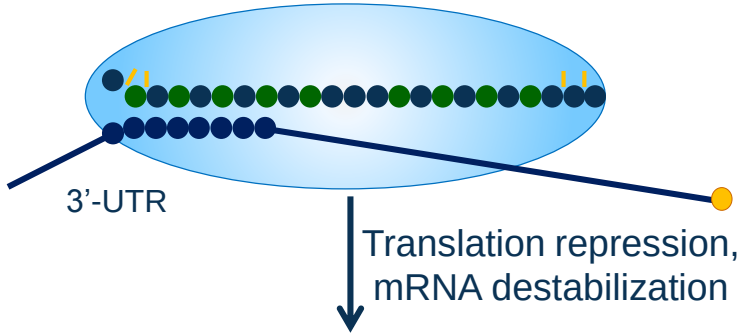
Advancing Larger Market Opportunities

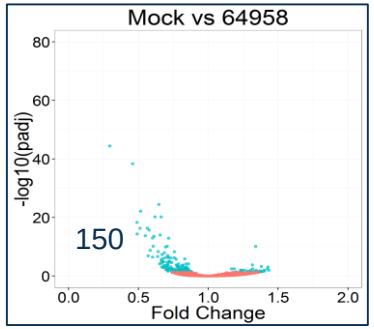
Optimizing Safety Profile

Transitioning Platform from ESC to ESC+

“Noisy” siRNA

miRNA-like seed mediated binding to off-targets



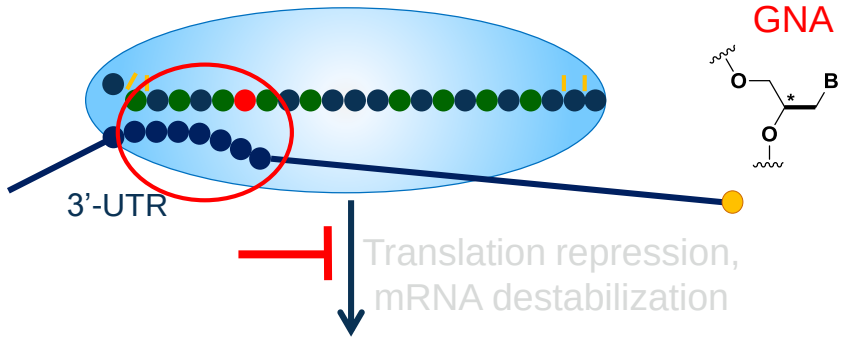


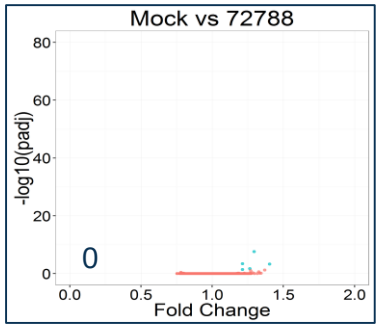
Seed enriched off-target effects observed

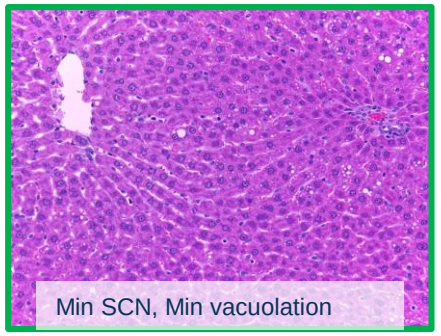
Rat NOAEL: 10 mg/kg

ESC+ Conjugate

Destabilize seed-mediated binding to off-targets; retain on-target activity







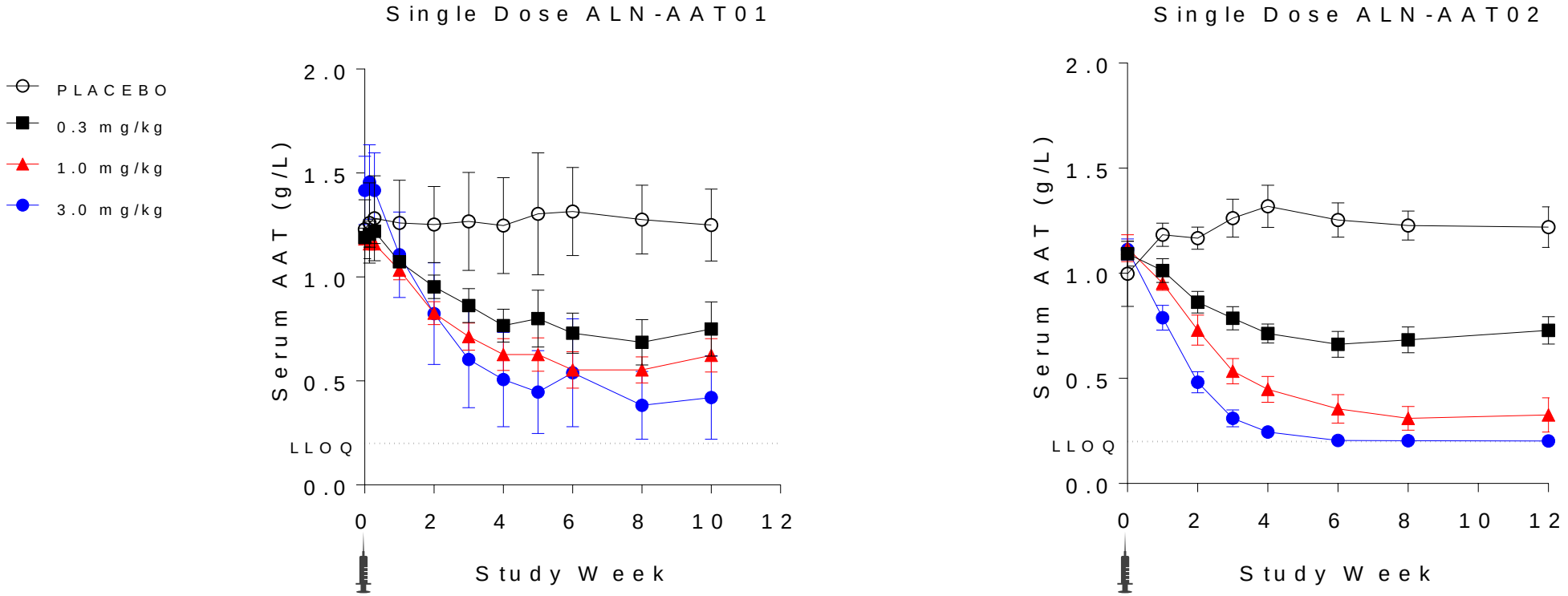
No off-targets effects observed

Rat NOAEL: 120 mg/kg

Janas et al, Nature Communication, 2018

Positive ESC+ Human POC

ALN-AAT02 Clinical Activity and Safety

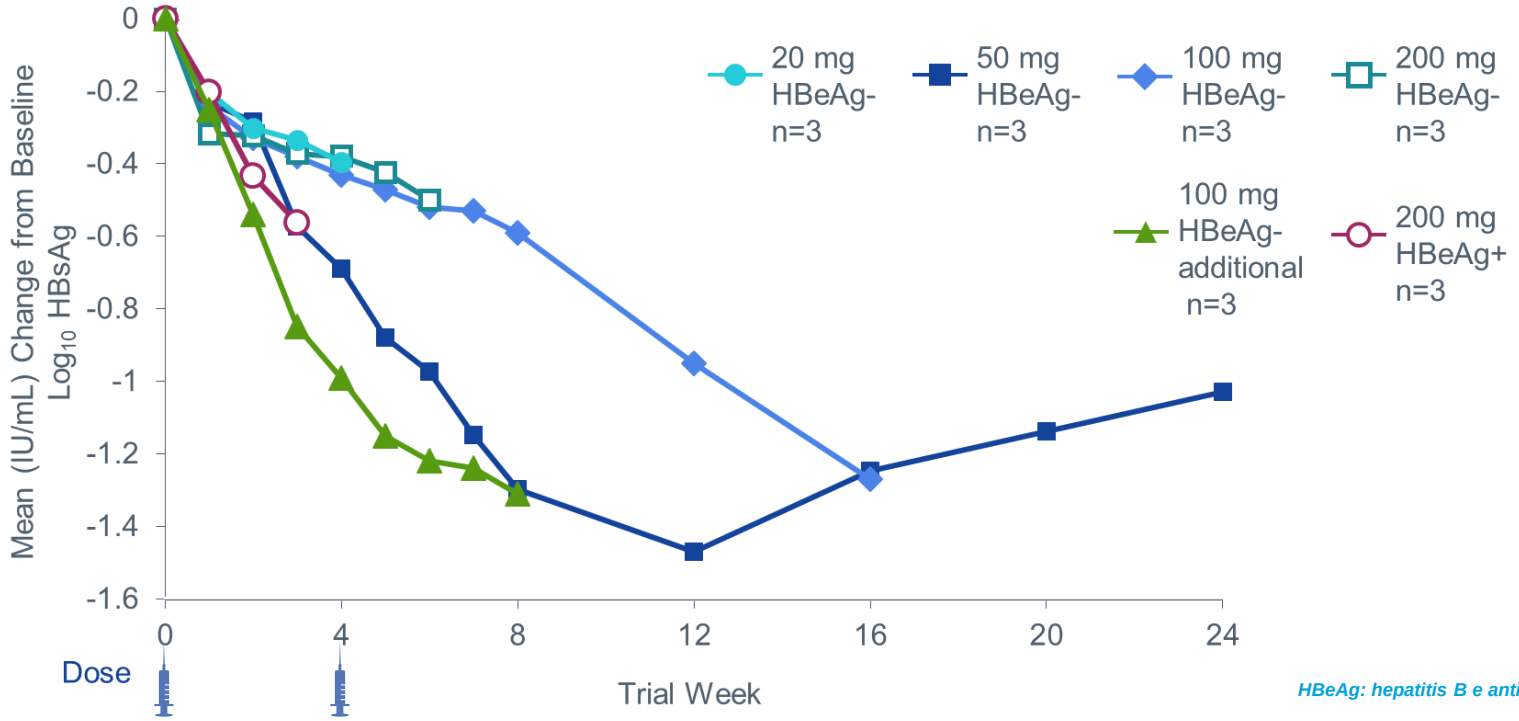


	ALN- AAT01	ALN-AAT02
Structure*		
Efficacy	Up to **89% KD**	Up to **89% KD**
Liver Safety (ALT >3x ULN)	**1/15** (up to 6 mg/kg dose)	**0/18** (up to 6 mg/kg dose)

* Images are representative

Positive ESC+ Human POC

VIR-2218 (ALN-HBV02) Mean Change in HBsAg



HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen.
Vir Biotechnology SEC filing

	ALN- HBV01 (HVs)	ALN-HBV02 (CHB Patients)
Structure*		
Efficacy	N/A	Up to **2.3log$_{10}$ reduction** in HBsAg
Liver Safety (ALT >3x ULN)	**2/18** (up to 3 mg/kg dose)	**0/31** (up to ~10 mg/kg dose)

* Images are representative

Evolving the Pipeline

Strategic Priorities

Building the Pipeline

Optimizing Safety Profile

Advancing Larger Market Opportunities

Advancing Larger Market Opportunities

Hypertension

Hypertension

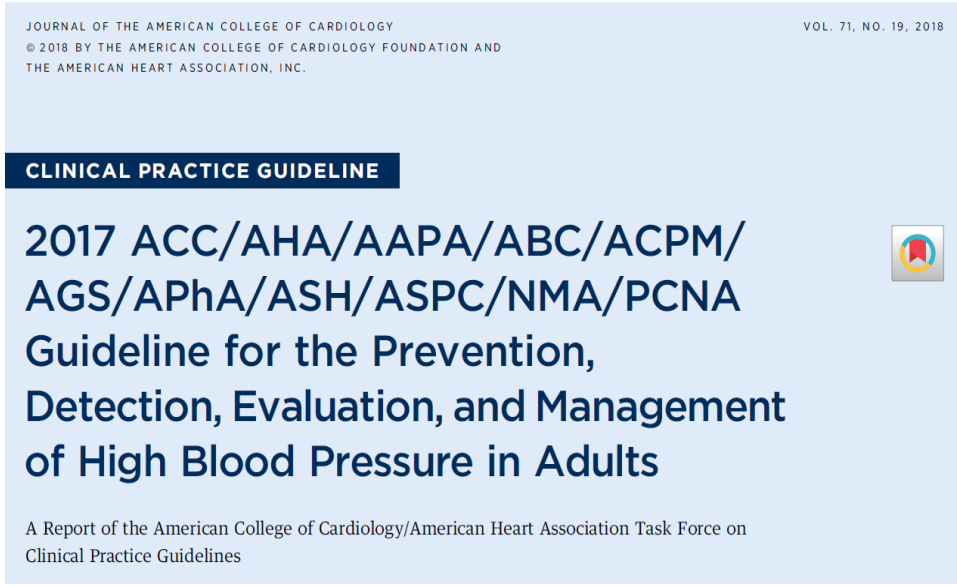
- Complex multifactorial disease
  - >100 genetic loci implicated
  - Diet (salt), weight and lifestyle contribute
- Defined as systolic blood pressure (SBP) >130 mmHg, or diastolic blood pressure (DBP) >80 mmHg

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

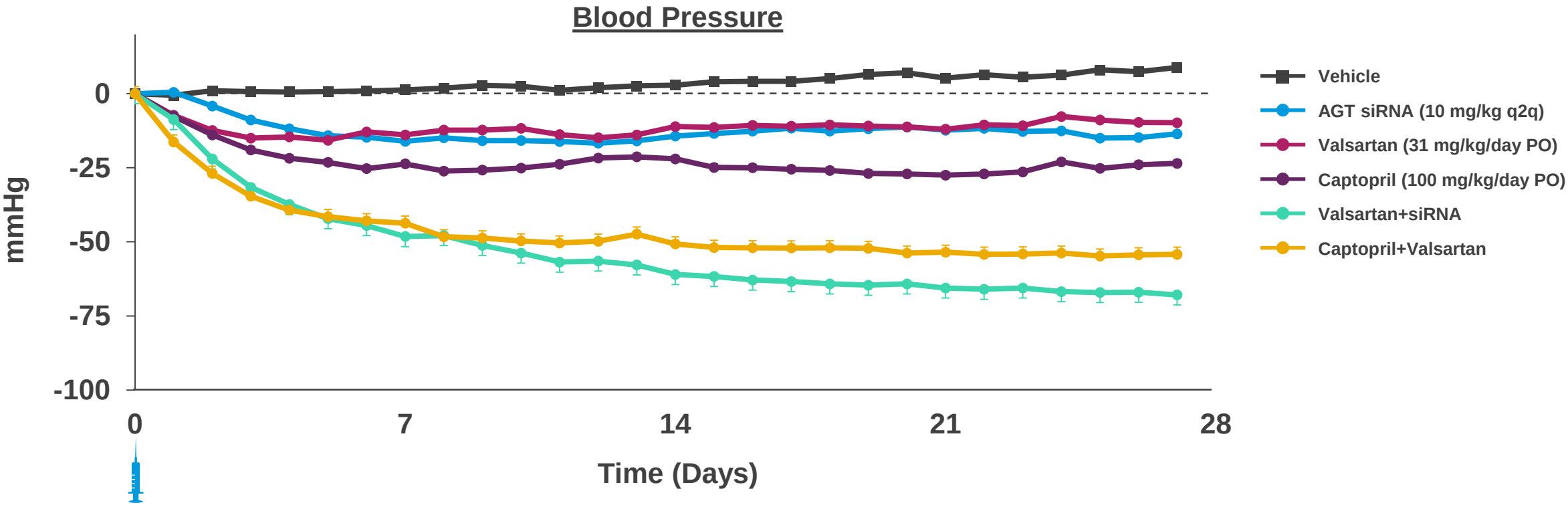
- 45.6% of U.S. adults have hypertension under 2017 ACC/AHA guidelines, with more than half of patients on medication remaining above BP target
- Despite availability of antihypertensives:
  - Poor adherence rates
  - Peak/trough effects
  - Resistant and refractory hypertension
  - In 2015, high BP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

ALN-AGT in Development for Hypertension

Angiotensinogen Silencing Results in BP Lowering in Rat Hypertension Model

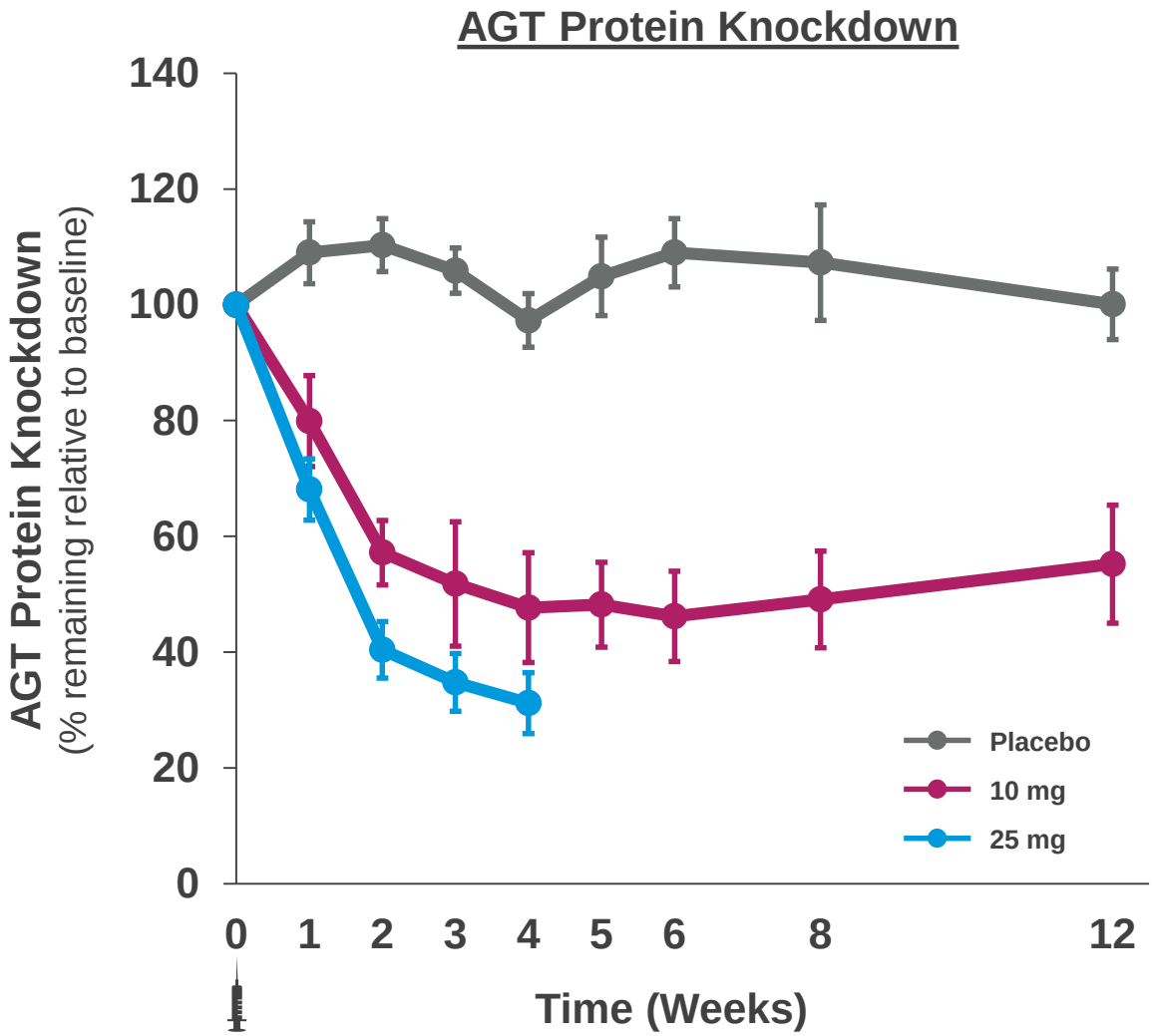


- **AGT siRNA reduced BP**
- **Combination of AGT siRNA + valsartan resulted in synergistic BP reduction, greater than captopril + valsartan**
  - Well tolerated, with no decrease in EGFR
- **Only AGT siRNA plus valsartan normalized cardiac hypertrophy**

Uijl E, Mirabito Colafella KM, Sun Y, et al. Strong and Sustained Antihypertensive Effect of Small Interfering RNA Targeting Liver Angiotensinogen. Hypertension. 2019;73(6):1249–1257. doi:10.1161/HYPERTENSIONAHA.119.12703

Dose-Dependent AGT Lowering in Patients with Essential Hypertension

Initial Results from Ongoing Phase 1 Study of ALN-AGT



- **Mean maximum AGT lowering of 59% at 10 mg dose (n = 8) and 69% at 25 mg dose**
- **Maximum AGT reduction achieved by 4 weeks & maintained for close to 12 weeks after 10 mg single dose**

Agenda

Progress to Date

Evolving the Pipeline

Future Outlook

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.

Potential of RNAi Therapeutic Platform

Comparison of Industry Trial Metrics to Alnylam Portfolio

Probability of Success (POS) by Phase Transition

	% POS Phase 1 to 2 (N)	% POS Phase 2 to 3 (N)	% POS Phase 3 (N)	% POS Cumulative
Industry overall*	35.2 (21,255)	27.4 (15,099)	59 (7,552)	**5.5**
Industry biomarker-driven programs*	44.5 (1,213)	38.6 (840)	60.2 (123)	**10.0**
Alnylam**	83.3 (12)	87.5 (8)	75 (4)	**54.6**

Factors likely contributing to higher rates of Alnylam success

- All programs start against genetically validated target (vs. historical industry rate of 2%)*
- Biomarkers integral to all programs (vs. historical industry rate of 7%)*
- Phase 1 data on target engagement and appropriate dose/regimen for further development

* Wong et al., Biostatistics (2019) 20, 2, pp. 273–286

** Alnylam programs biomarker-driven at all stages of development (100%)

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 early 2020

- 50K exomes sequenced to date

Contributions to R&D Strategy

Access new targets

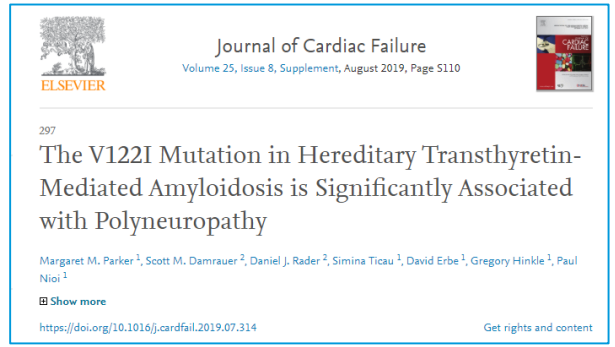
- ~800 genes with homozygous or heterozygous loss-of-function (human KO) observed in at least 1 individual
  - Rich source of potential targets based in protective phenotypes associated with loss-of-function alleles
  - Identify targets for bispecific RNAi therapeutics
  - Rapidly validate targets reported in literature

Extend target populations for current programs

- Givosiran
- Lumasiran

Understand phenotypes for diseases of interest

- V122I commonly associated with polyneuropathy
- T119M not protective against cerebrovascular disease


Journal of Cardiac Failure
Volume 25, Issue 8, Supplement, August 2019, Page S110

297

The V122I Mutation in Hereditary Transthyretin-Mediated Amyloidosis is Significantly Associated with Polyneuropathy

Margaret M. Parker [1], Scott M. Damrauer [2], Daniel J. Rader [2], Simina Ticau [1], David Erbe [1], Gregory Hinkle [1], Paul Nioi [1]

Show more

https://doi.org/10.1016/j.cardfail.2019.07.314

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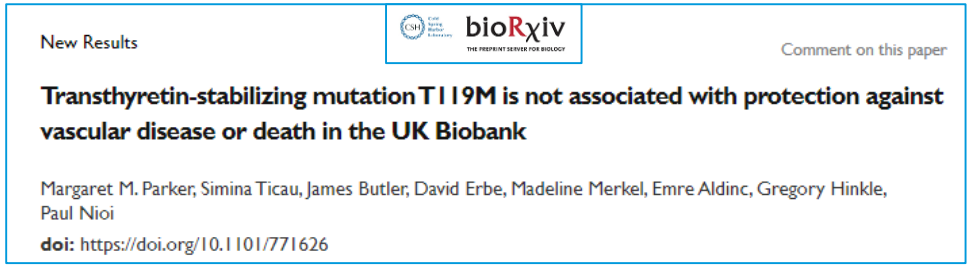

New Results

bioRxiv

Comment on this paper

Transthyretin-stabilizing mutation T119M is not associated with protection against vascular disease or death in the UK Biobank

Margaret M. Parker, Simina Ticau, James Butler, David Erbe, Madeline Merkel, Emre Aldinc, Gregory Hinkle, Paul Nioi

doi: https://doi.org/10.1101/771626

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

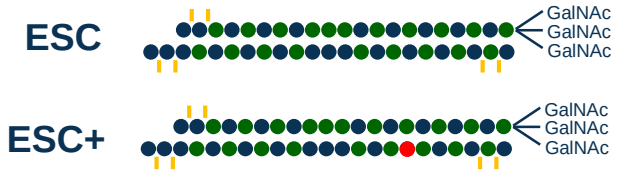
ORIGINAL ARTICLE

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

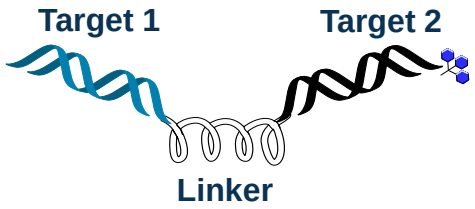
P. Nioi, A. Sigurdsson, G. Thorleifsson, H. Helgason, A.B. Agustsdottir, G.L. Norddahl, A. Helgadottir, A. Magnusdottir, A. Jonasdottir, S. Gretarsdottir, I. Jonsdottir, V. Steinthorsdottir, T. Rafnar, D.W. Swinkels, T.E. Galesloot, N. Grarup, T. Jørgensen, H. Vestergaard, T. Hansen, T. Lauritzen, A. 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

RNAi Platform Advances

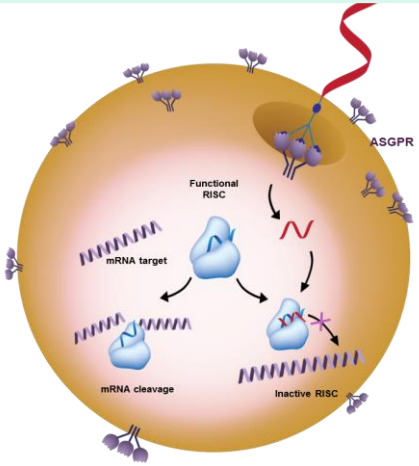
ESC+ Design: Improved Specificity and Safety in Humans



Bis-RNAi™: Single Chemical entity for simultaneous silencing of two transcripts



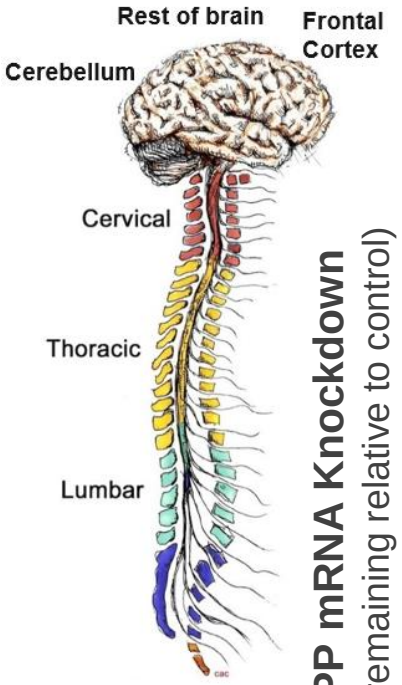
Reversir™: Tailored Control of RNAi Pharmacology by Rapid Reversal of Target Silencing



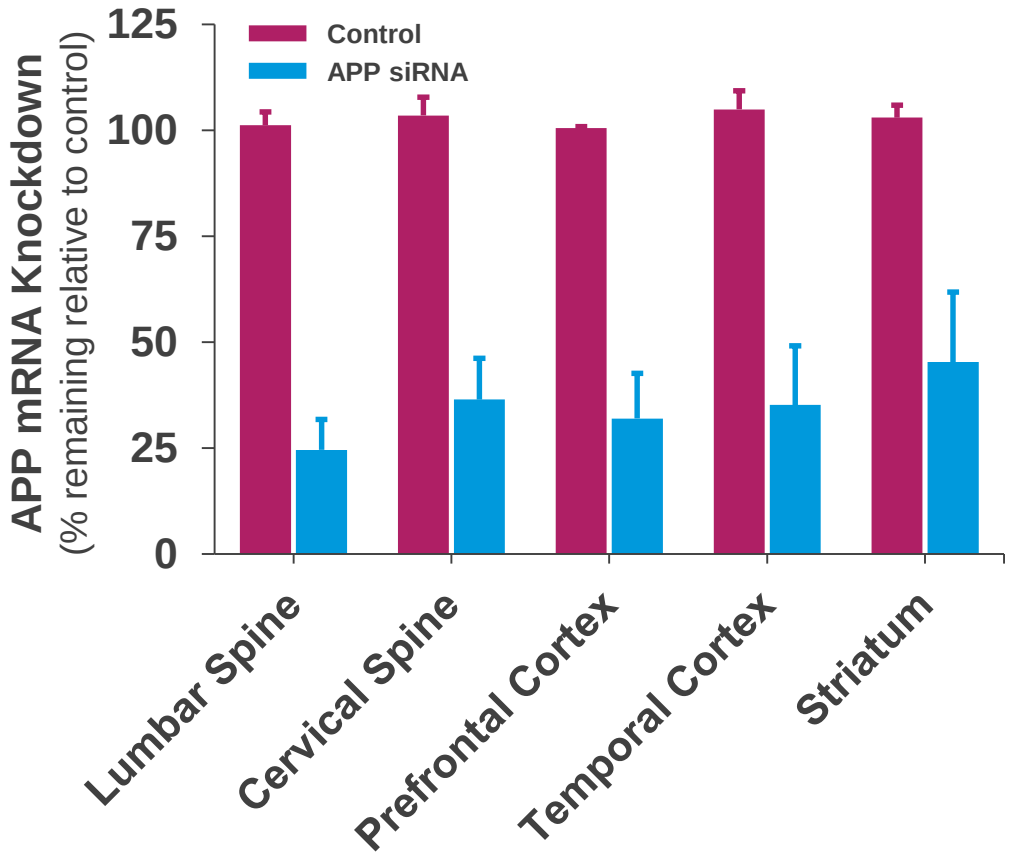
Extrahepatic Delivery: RNAi Rx for CNS and Ocular Diseases

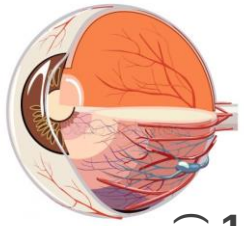
Oral Delivery

Robust Silencing of CNS and Ocular Targets

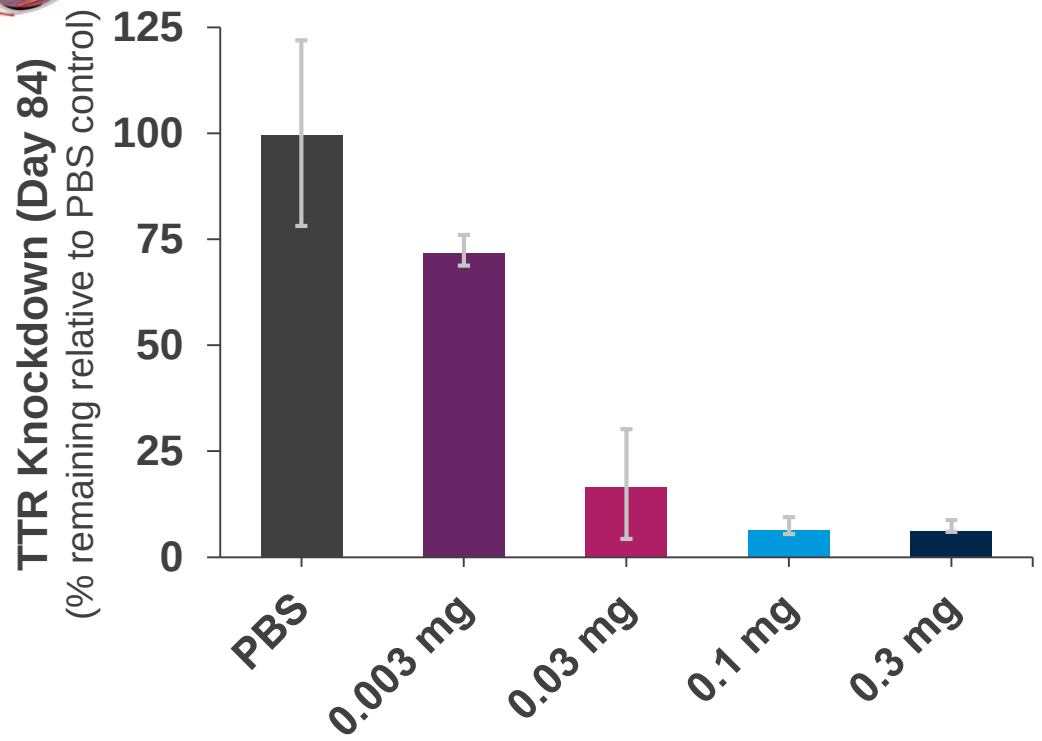


CNS APP mRNA Knockdown (Single Intrathecal Dose in NHP)





Ocular TTR Protein Knockdown (Single Intravitreal Dose in NHP)



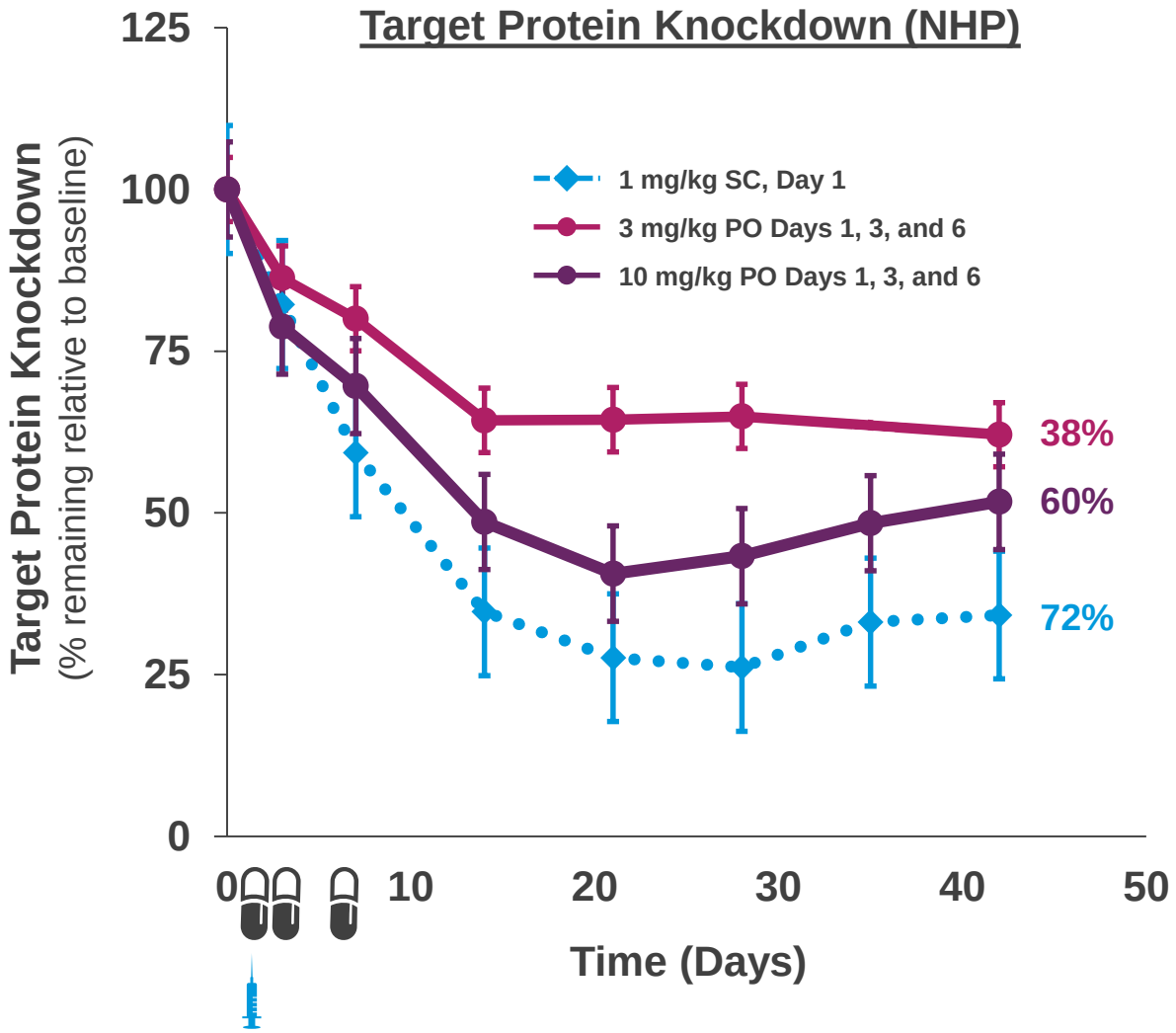
Alnylam-Regeneron Alliance

Landmark Alliance Focused on CNS & Ocular RNAi Therapeutics

- Partnership of two leading biopharmaceutical companies committed to innovation
  - Alnylam R&D expertise and scientific excellence in RNAi therapeutics with emerging global commercial presence
  - Regeneron scientific excellence, world-leading capabilities in human genetics, and industry-leading commercial presence in ophthalmology and other large markets
- Broad, multi-product alliance across CNS, ocular, and select liver targets
  - Both companies fully participate in value creation with 50-50 structure in CNS and select liver programs
  - Milestone/royalty structure for ocular disease programs
- Accelerates Alnylam CNS and ocular programs, driving significant pipeline expansion
  - Robust, highly durable, and widely distributed RNAi knockdown of key targets in CNS/ocular pre-clinical models
  - Adds 1-2 new planned INDs/year toward CNS or ocular targets to previously planned 1-2 new INDs/year in liver
- Provides significant financial support for increased pipeline investment and future growth

Achieved PoC for Oral Delivery in NHP

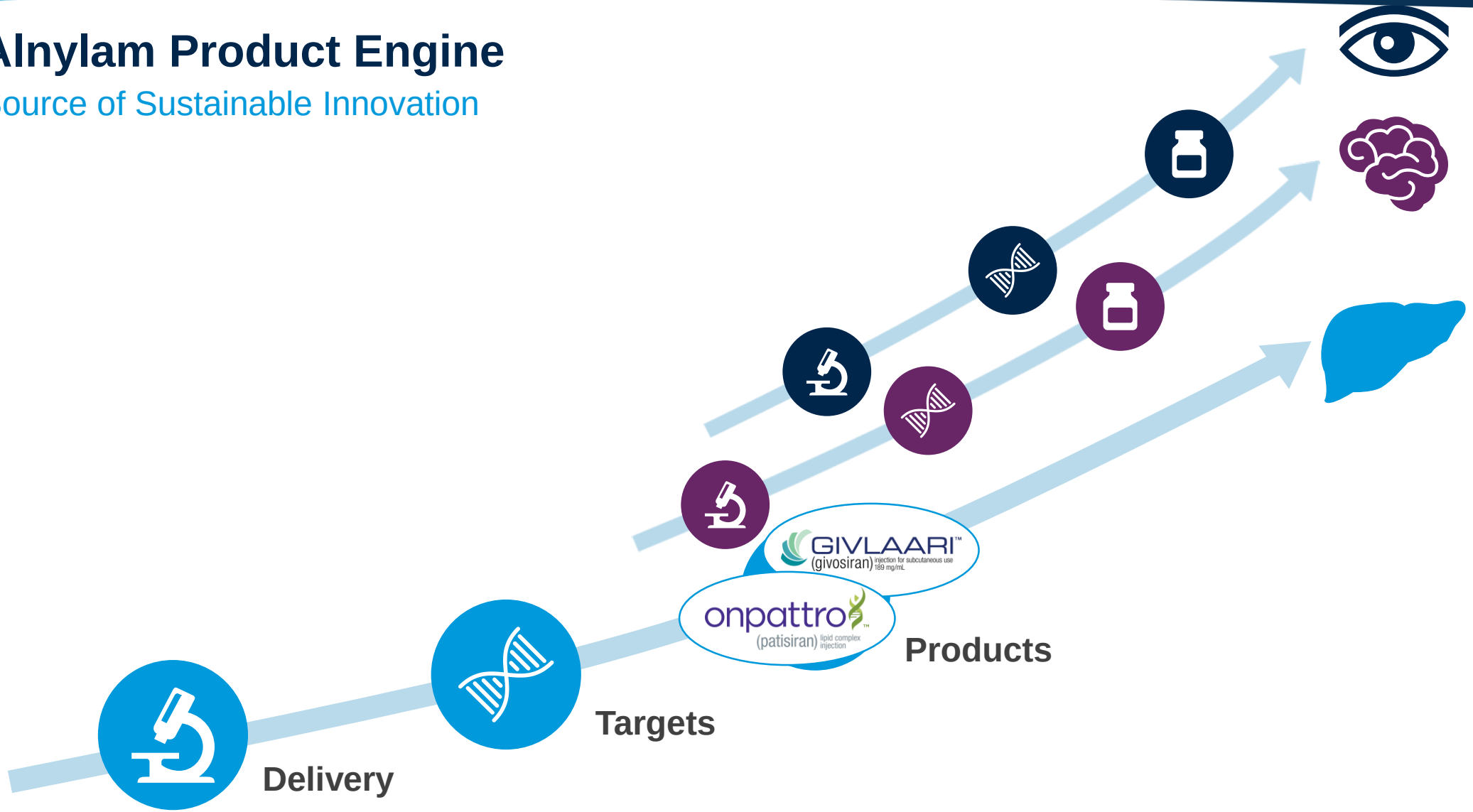
Dose Dependent, Durable KD with Minimal Variability Similar to SC Dosing



- First ever *in vivo* demonstration of oral delivery of RNAi therapeutic
- Creates optionality for clinical pipeline, especially for large indications
- Potential for high potency, low frequency Q3M-Q6M dosing, similar to subcutaneous dosing
- Optimization in progress

Alnylam Product Engine

Source of Sustainable Innovation



Transthyretin (TTR) Amyloidosis

Eric Green, SVP & General Manager, TTR Program
Pushkal Garg, M.D., Chief Medical Officer

Alnylam® PHARMACEUTICALS

Transthyretin (TTR) Amyloidosis

ONPATTRO® (patisiran) and Vutrisiran

ONPATTRO Program Update

- Eric Green, SVP & General Manager, TTR Program

Cardiac Amyloidosis: A New Paradigm

- Nitasha Sarswat, M.D., Director, Infiltrative Cardiomyopathy Program
  University of Chicago Medicine

Expanding the ATTR Opportunity

- Pushkal Garg, M.D., Chief Medical Officer

ATTR Amyloidosis

Rare, Progressively Debilitating, and Often Fatal Disease

Caused by misfolded TTR protein that accumulates as amyloid deposits in multiple tissues including heart, nerves, and GI tract[1]

Hereditary ATTR (hATTR) Amyloidosis

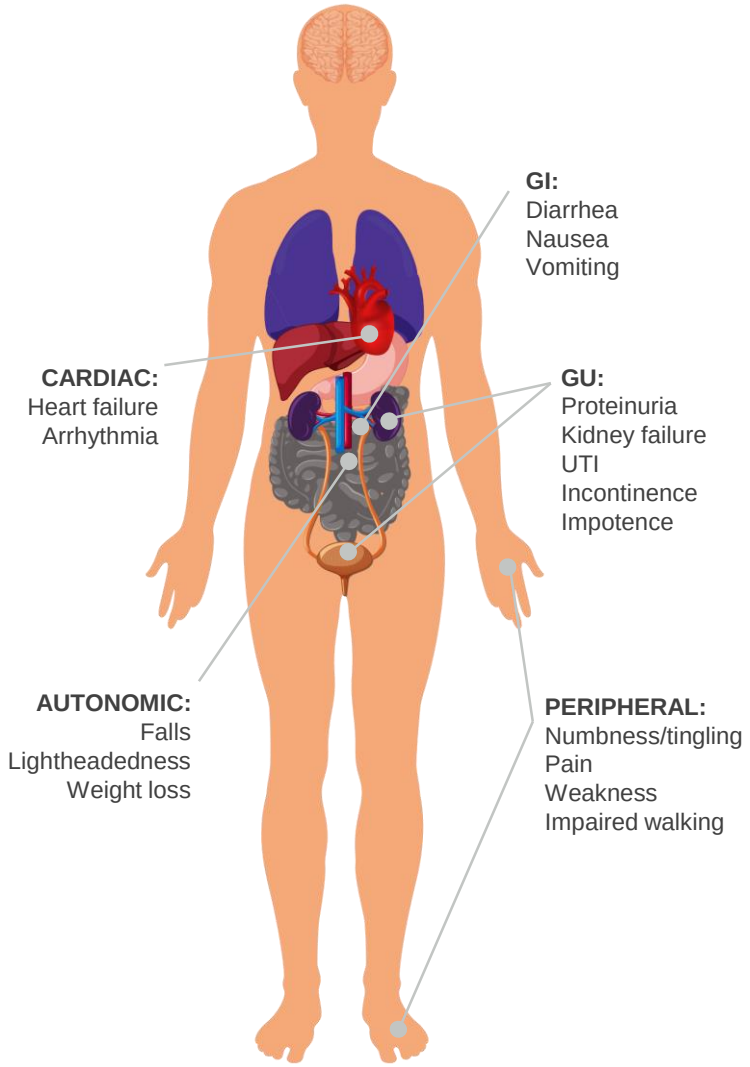
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

patients worldwide



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

Strategic Framework for ONPATTRO Growth

Multiple Factors to Drive Planned Steady and Continued Growth for ONPATTRO^

New Patient Finding

Global Expansion

Evidence Generation

^ ONPATTRO is approved in the United States and Canada for the treatment of the polyneuropathy of hATTR amyloidosis in adults, in the EU and Switzerland for hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, and in Japan for transthyretin (TTR) type familial amyloidosis with polyneuropathy; for additional information on ONPATTRO, see Full Prescribing Information

Strategic Framework for ONPATTRO Growth

Expect Continued Growth in Current Markets to Be Driven by New Patient Finding

New Patient Finding

Global Expansion

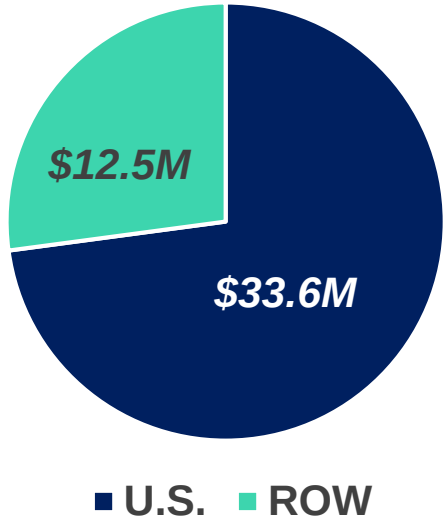
Evidence Generation

ONPATTRO Global Launch Update: Q3 2019

Strong Performance with Significant Growth Potential

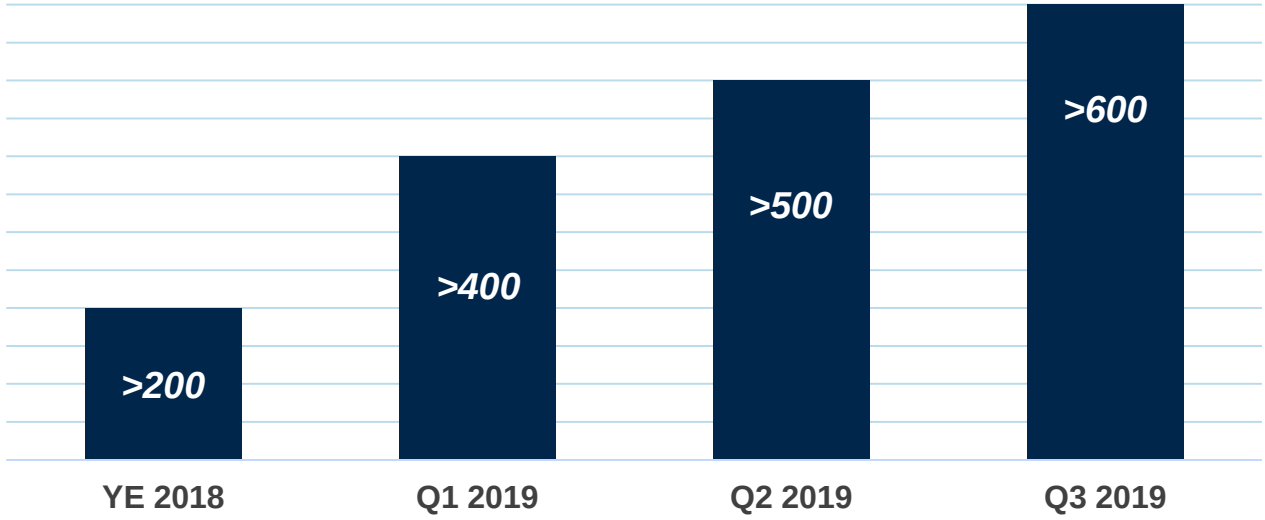
$46.1M

ONPATTRO Global Q3
Net Product Revenues



>600

Patients Worldwide on Commercial
ONPATTRO at Q3 2019



Expect steady and continued growth with new patient finding, global expansion, and evidence-generating activities

U.S. ONPATTRO Demand/Adherence, Prescriber Mix, and Access

Selected Metrics Launch Through Q3 2019

>200	Unique prescribing physicians*
41%	Demand from neurologists*
41%	Demand from cardiologists*
18%	Demand from other specialties*
>90%	Adherence on commercial ONPATTRO
98%	U.S. lives with confirmed access to ONPATTRO, if prescribed†

* Based on total Start Forms submitted through Q3 2019. Start Forms are an incomplete picture of U.S. demand.

† Across commercial, Medicare, Medicaid, and other government payer categories (DKP PayerScope® August 1, 2018 through September 30, 2019).

U.S. Patient Perspectives on ONPATTRO

Positive Customer Experiences in First Year of Launch

80%

of U.S. patients have zero cost-share for ONPATTRO[1]

>85%

of patients enrolled in Alnylam Assist, our patient services support program

4.8 out of 5

Recent satisfaction score from patients on Alnylam Assist®

"Everyone has been so helpful with every problem and concern. Really glad to have the help and support."

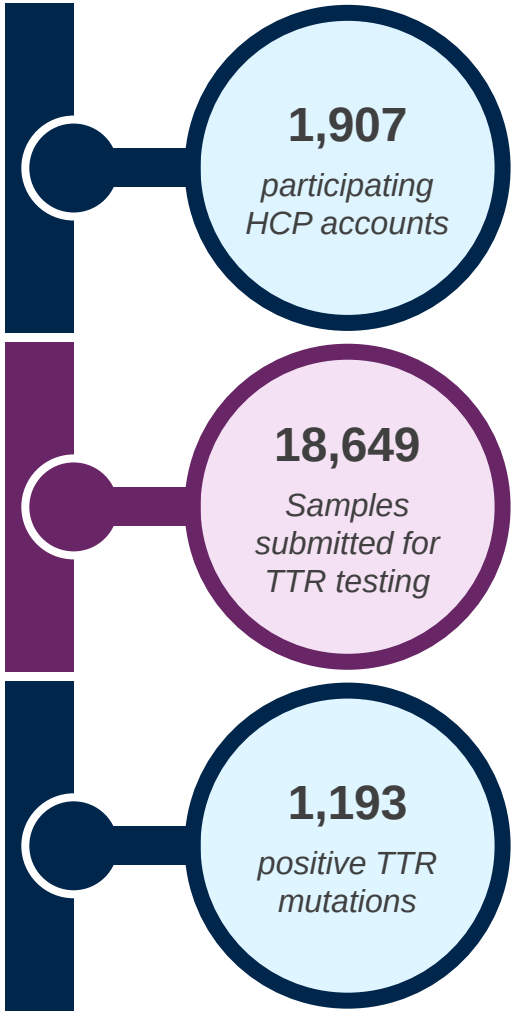
"Very informative. Allowed me to meet others so I don't feel all alone. Also was great for my caregiver to have a better understanding of the disease and the medicine."

Data through Jun 30, 2019; www.alnylam.com/wp-content/uploads/pdfs/Alnylam-Patient-Access-Philosophy-Report.pdf

1 Includes patients receiving commercial co-pay support, as well those patients with Managed Medicare or Medicare FFS plus supplement

Alnylam Act® – hATTR Amyloidosis

Third-Party Genetic Testing and Counseling Program Sponsored by Alnylam



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

Tests and services are performed by independent third parties

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

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

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

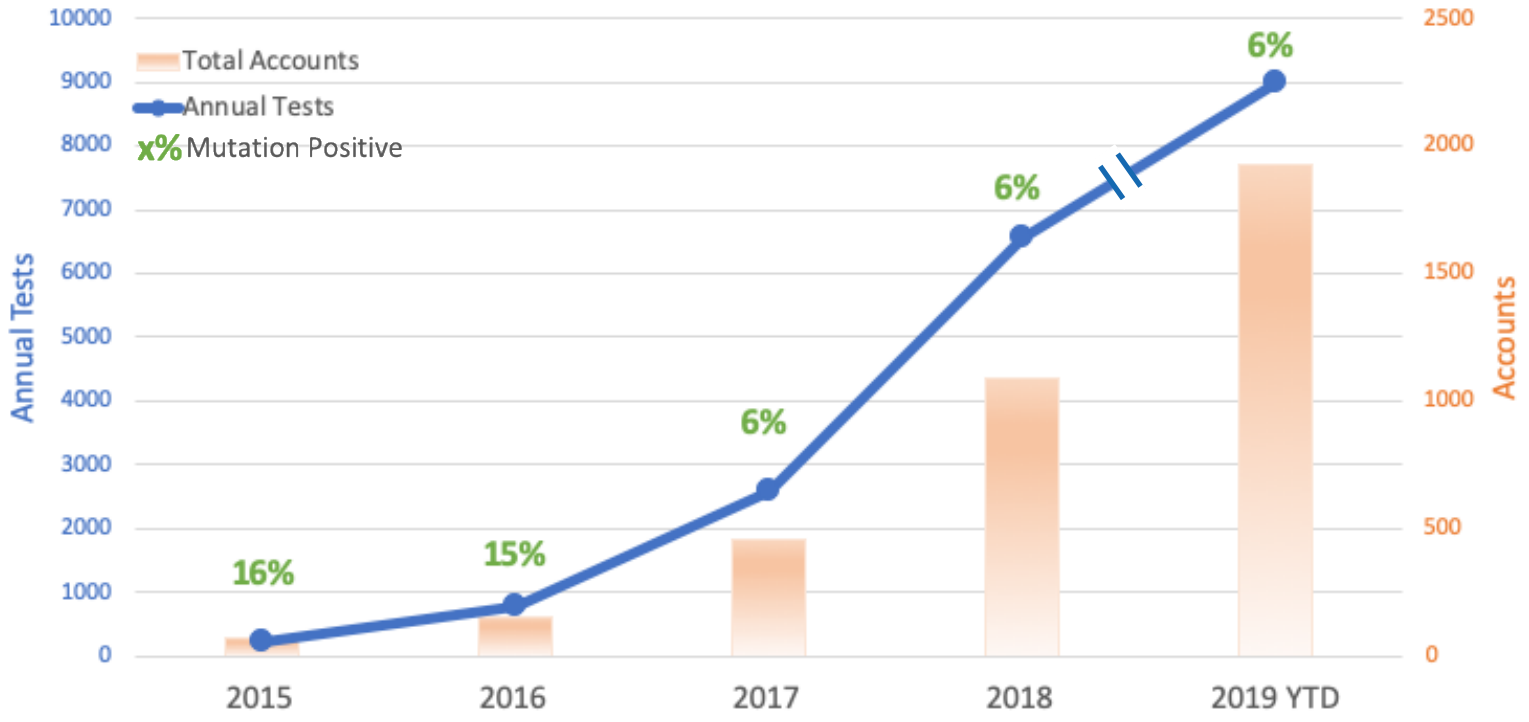
Data as of October 2019

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

Alnylam Act – hATTR Amyloidosis

Five Years of Support for Patients and Improved Diagnosis

- Percentage of tests with positive mutations remained steady as volume increased



- Testing results consistent with prevalence estimates in U.S.

67%	V122I
11%	T60A
10%	V30M
12%	Other

Data as of Oct 2019

Strategic Framework for ONPATTRO Growth

Additional Growth Driven by Planned Access to New Markets

New Patient Finding

Global Expansion

Evidence Generation

ONPATTRO Market Approvals and Submissions

With Global Rights, Bringing ONPATTRO to Patients Around the World

	**U.S.**	*August 10, 2018*	For the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
	**EU**	*August 27, 2018*	For the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults with stage 1 or stage 2 polyneuropathy
	**Canada**	*June 7, 2019*	For the treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis)
	**Japan**	*June 18, 2019*	For the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy
	**Switzerland**	*September 23, 2019*	For the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults with stage 1 or stage 2 polyneuropathy

Israel Filing

MAA submitted June 2019

Brazil Filing

NDA submitted October 2019

Successfully Navigating Pricing and Reimbursement in CEMEA

Pricing and Reimbursement in Additional Countries Expected to Drive 2020 Growth

- Positive HTA recommendations
- Commercially available via private insurance
- Negotiations with Provinces begin Q4’19

- Reimbursed in NL, BE and LU
- Commercially available

- NICE and SMC approval
- Commercially available, including home care

- DE: “Considerable” benefit rating with negotiated rebate among lowest of all orphan drugs; Commercially available
- AT: Commercially available

- Positive ASMR III rating
- Available through ATU program
- Negotiations for official P&R ongoing

- P&R negotiations ongoing
- Available via reimbursed named patient access

- Successful clinical / HTA assessment
- P&R negotiations ongoing
- Available through reimbursed named patient access

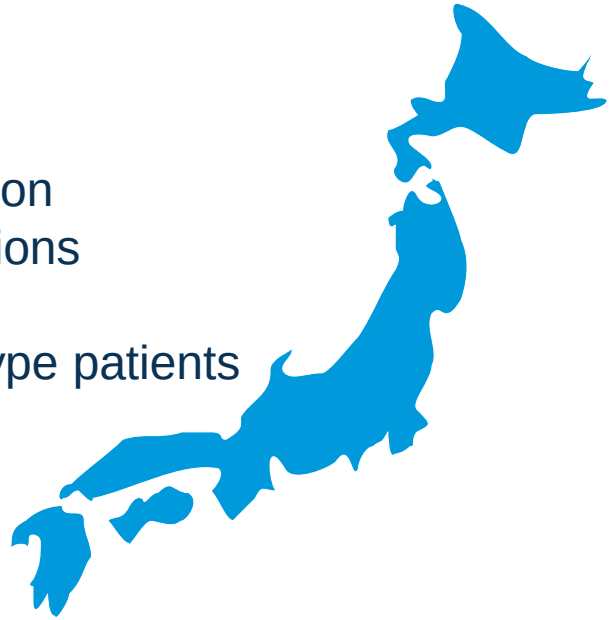
- Supporting Central & Eastern Europe through distributors; significant P&R progress to-date
- P&R discussions ongoing in multiple other EU markets: Portugal, Ireland, Switzerland, Denmark, Sweden

CEMEA: Canada, Europe, Middle East, North Africa; ATU: Temporary Authorization for Use; ASMR: Amélioration du service médical rendu

Significant Opportunity for ONPATTRO in Asia and Latin America

Driving Global Expansion

Japan



- Endemic V30M population concentrated in two regions
- Primarily mixed phenotype patients
- Two key centers of excellence
- Strong initial launch by Alnylam team
- Potential to be second largest ONPATTRO country in terms of number of patients and revenue by end of 2020

Brazil

- Endemic V30M population in southeast region and emerging awareness of V122I
- Mixed phenotype in majority of patients
- Regulatory filing under priority review
- Expect decision from ANVISA in mid-2020
- Building focused Alnylam team, gated to key milestones

Strategic Framework for ONPATTRO Growth

Continued Investment in Development of Patisiran

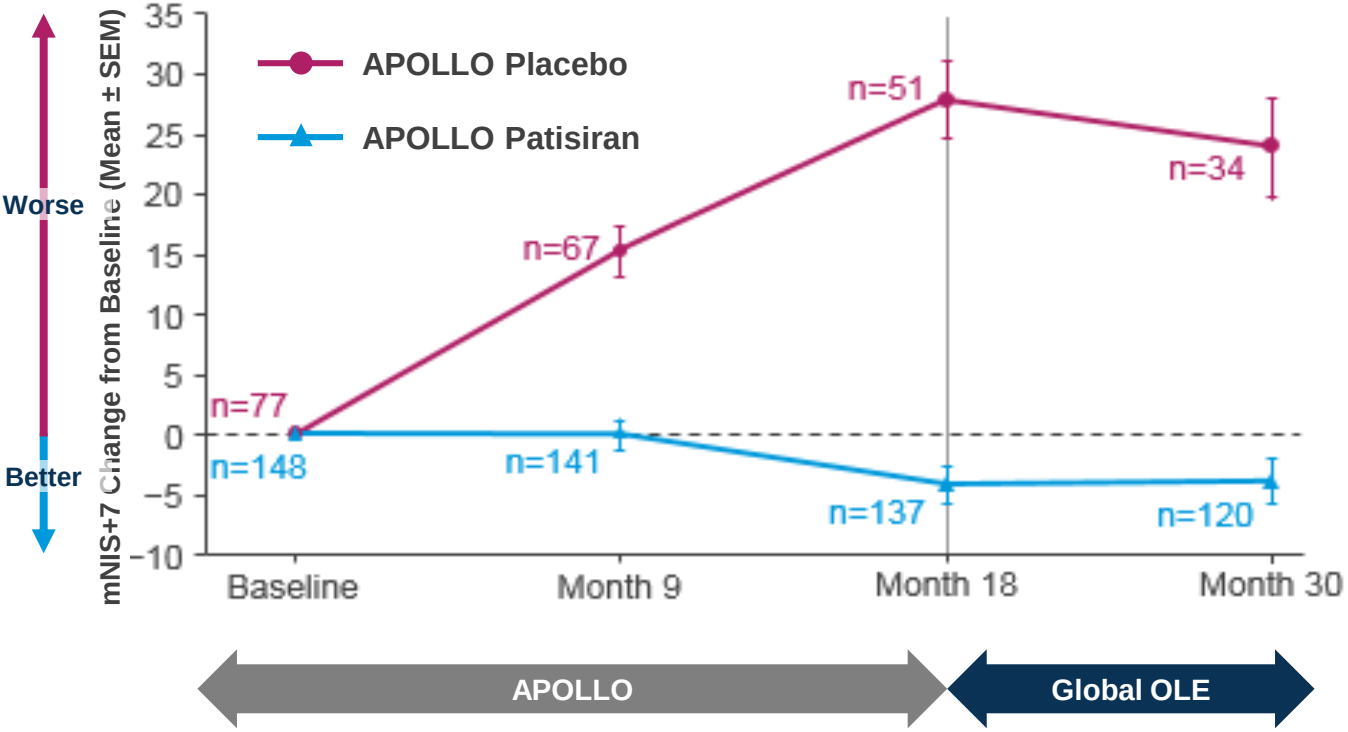
New Patient Finding

Global Expansion

Evidence Generation

Reversal of Polyneuropathy Manifestations Relative to Baseline Maintained in Global OLE with Consistent Safety Profile

Integrated Change in mNIS+7 from APOLLO and Global OLE[a]



Safety profile remained consistent with previous studies

Integrated Exposure Adjusted Mortality Rates[c]

	APOLLO Placebo n=49	APOLLO Patisiran n=148	Phase 2 OLE Patisiran n=27	Global OLE Total n=224
Deaths[b], n (%)	13 (27)	15 (10)	2 (7)	30 (13)
Exposure-Adjusted Mortality Rate (CI), deaths per 100 patient-years	**18.9** (10.4, 31.2)	**3.4** (2.0, 5.4)	**1.7** (0.3, 5.2)	**4.8** (3.3, 6.7)

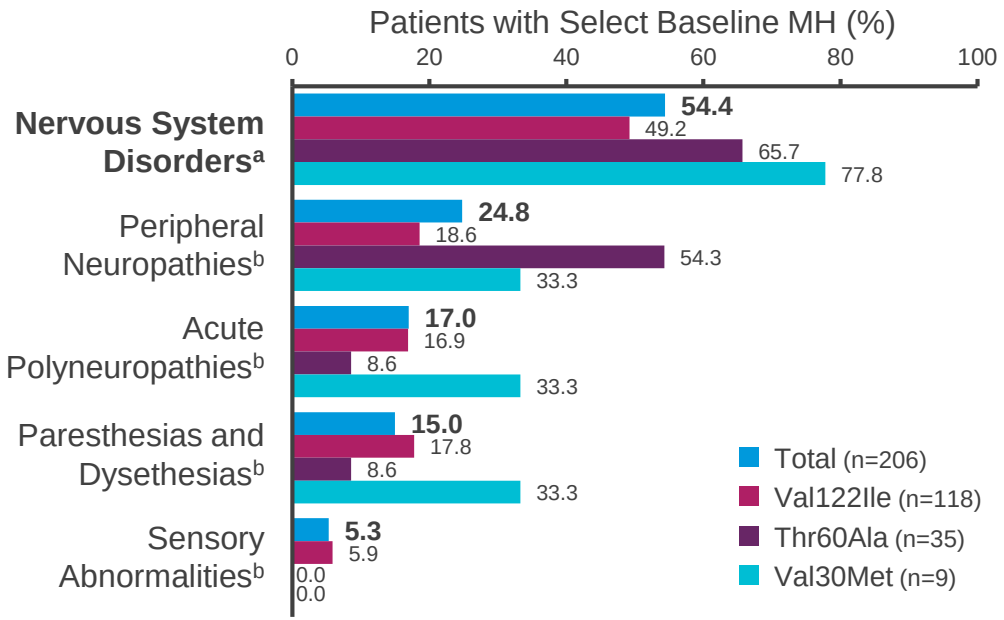
a For APOLLO patients initiating alternative hATTR amyloidosis treatment, mNIS+7 assessments after alternative treatment are treated as missing; bAll deaths summarized, including deaths due to AEs that are not treatment-emergent; cIn this group, 1 additional patient with breast cancer died 6.5 months after withdrawing from the study

Polydefkis, PNS, June 2019: Long-term Safety and Efficacy of Patisiran in Patients with hATTR Amyloidosis: Global OLE Study

Identifying Mixed Phenotype in hATTR Amyloidosis[1]

Identifying Early Signs / Symptoms Crucial to Expedite Diagnosis of this Multi-System Orphan Disease

Select Baseline Medical History in Patients with hATTR Amyloidosis



For nervous system disorders (SMQ for peripheral neuropathy), HLTs are shown that were >5% in the total population
[a]MedDRA SOC; [b]MedDRA HLT

Study Conclusions

- In hATTR amyloidosis patients with confirmed cardiomyopathy, **polyneuropathy symptoms found in ≥50% of patients**
- Medical history of **neuropathy tended to precede or coincide with signs and symptoms of cardiomyopathy**, even in V122I patients
- **Polyneuropathy may be an early sign** potentially overlooked in patients with hATTR amyloidosis with cardiomyopathy
- Due to debilitating and fatal nature of this disease, **identification of early signs and symptoms crucial to expedite diagnosis of hATTR amyloidosis**

1 Grogan, HFSA, Sep 2019. Identifying Mixed Phenotype: Evaluating the Presence of Polyneuropathy in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Cardiomyopathy

Baseline characteristics and medical history collected during screening period from a Phase 3 study of hATTR amyloidosis with cardiomyopathy (NCT02319005) were analyzed in overall study population and three most commonly occurring mutations to evaluate presence of polyneuropathy signs and symptoms

Additional Evidence Generation Through Clinical Studies

Continued Evaluation of Patisiran in Phase 3b and Phase 4 Studies

Patisiran Post-OLT Ph 3b Study

- *Strategic Objective*: Evaluate efficacy and safety of patisiran in patients with hATTR amyloidosis with disease progression after liver transplant (N = 24)
- *Primary Endpoint*: Average of Month 6 and Month 12 TTR percent reduction
- Only investigational therapeutic to be studied specifically in this patient population
- Enrollment completed in Sep'19

Interim results expected
Early 2020

ONPATTRO V122I/T60A Ph 4 Study

- *Strategic Objective*: Provide real-world evidence in patients with hATTR amyloidosis with polyneuropathy with V122I or T60A mutation (N ~100)
- *Primary Endpoint*: Effect on ambulatory status (PND Score) at Month 12
- Most prevalent mutations in U.S.; predominantly cardiac involvement but often polyneuropathy symptoms as well
- Evaluate effectiveness across multisystem manifestations of disease

Study expected to initiate
Late 2019

Post-OLT Study ClinicalTrials.gov Identifier: NCT03862807
OLT: Orthotopic Liver Transplant; PND Score: Polyneuropathy Disability Score

Alnylam's TTR Amyloidosis Franchise

Approved and Investigational Treatment Options

onpattro® (patisiran) lipid complex injection 10 mg/5 mL

ONPATTRO (patisiran) is an **Approved** RNAi Therapeutic for Treatment of Polyneuropathy of hATTR Amyloidosis*

- Favorable efficacy and safety profile in APOLLO study
- Improvement in neuropathy impairment in majority of patients
- Improvement in quality of life in majority of patients

About ONPATTRO

- RNAi therapeutic targeting transthyretin (TTR)
- IV administration, once every 3 weeks
- Patisiran also in clinical development as potential treatment for ATTR amyloidosis patients with cardiomyopathy‡

Vutrisiran

Vutrisiran is an **Investigational** RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis†

- Potential treatment for hATTR amyloidosis with polyneuropathy (HELIOS-A study)
- Potential treatment for ATTR amyloidosis with cardiomyopathy (HELIOS-B study)

About Vutrisiran

- RNAi therapeutic targeting transthyretin (TTR)
- Subcutaneous administration, once every 3 months
- Pre-filled syringe (PFS) presentation

* ONPATTRO is approved in the U.S. and Canada for the treatment of the polyneuropathy of hATTR amyloidosis in adults, in the EU and Switzerland for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; ‡ 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 is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness

Building Leading TTR Franchise to Serve Patients for Years to Come

Vision: ONPATTRO Establishes Strong Foundation; Vutrisiran Achieves Sustainable Market Leadership

Benefits of franchise

Product revenue supports continued investment;

Vutrisiran launch (if approved) will utilize global ONPATTRO footprint

Patient and physician choice is key

Aim to provide options for patients and physicians

ONPATTRO will remain an attractive option

Many patients and HCPs will be well served by ONPATTRO and will choose to continue therapy

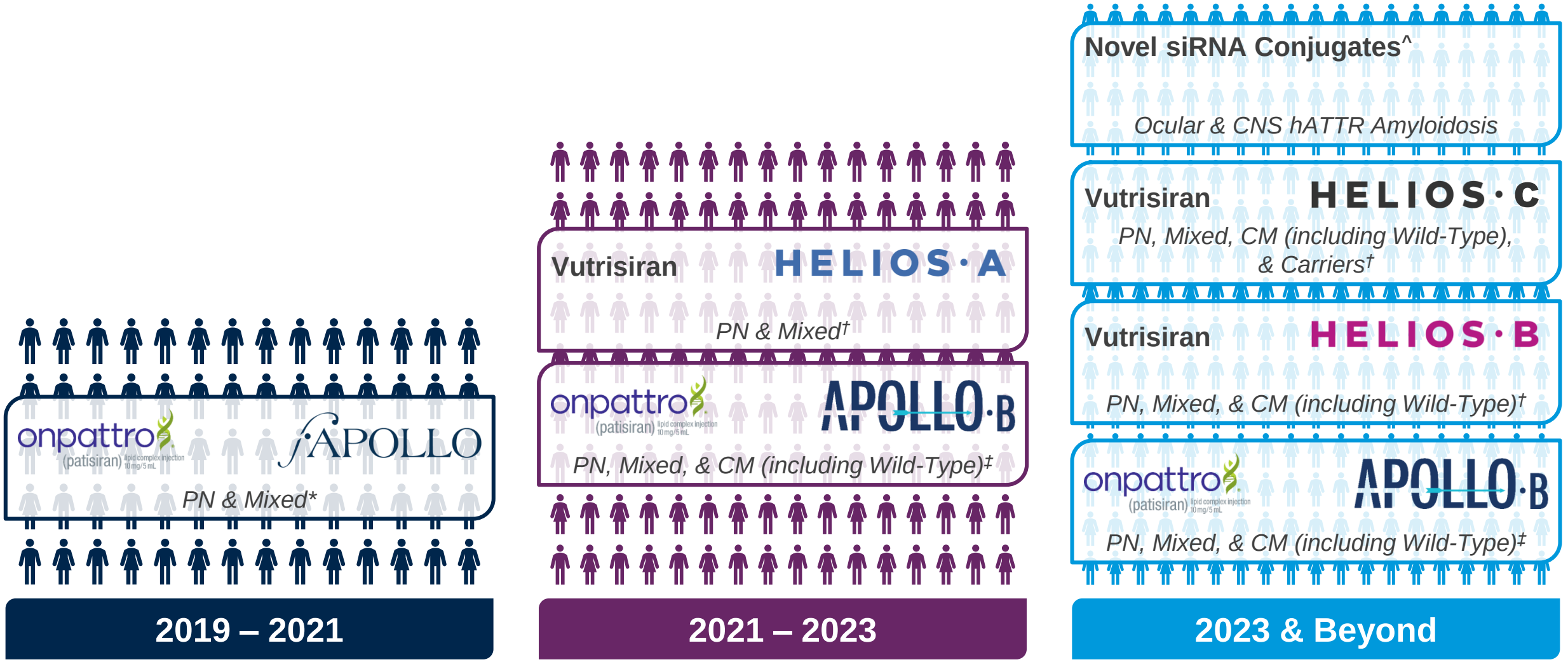
Vutrisiran target profile

Potential for most competitive product profile (efficacy, safety, dose/schedule)

Ensure broad access via continued innovation with payers

Alnylam ATTR Amyloidosis Franchise

Potential to Expand Value to Patients Globally for Many Years to Come



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† Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; additional studies and future development possible; ^ Novel siRNA conjugate development candidates for ocular or CNS hATTR amyloidosis not yet selected.

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

Transthyretin (TTR) Amyloidosis

ONPATTRO (patisiran) and Vutrisiran

ONPATTRO Program Update

- Eric Green, SVP & General Manager, TTR Program

Cardiac Amyloidosis: A New Paradigm

- Nitasha Sarswat, M.D., Director, Infiltrative Cardiomyopathy Program
  University of Chicago Medicine

Expanding the ATTR Opportunity

- Pushkal Garg, M.D., Chief Medical Officer

AT THE FOREFRONT

UChicago Medicine

Cardiac Amyloidosis: A New Paradigm

Nitasha Sarswat, MD

Director, Infiltrative Cardiomyopathy Program

Advanced Heart Failure, Mechanical Circulatory Support and Transplantation

University of Chicago Hospital

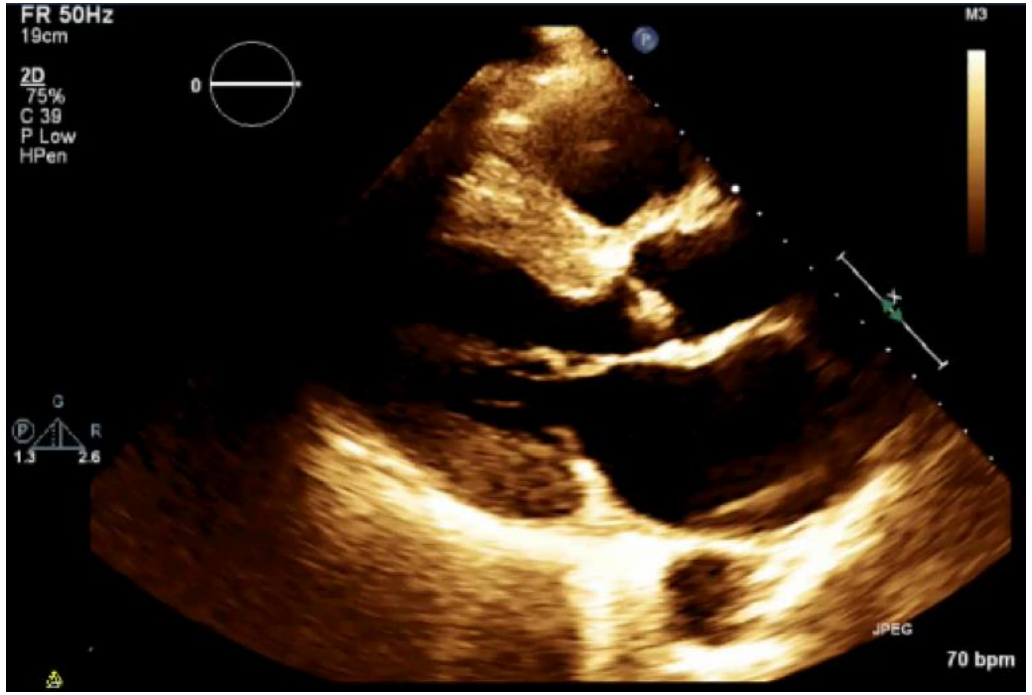
11/22/2019

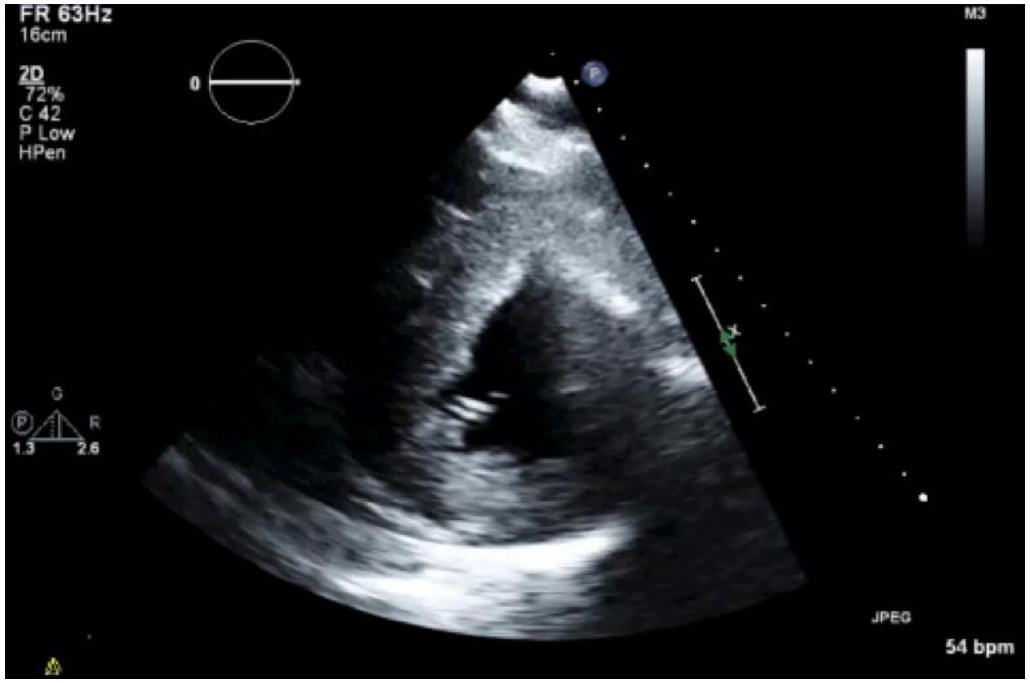
Goals of this discussion

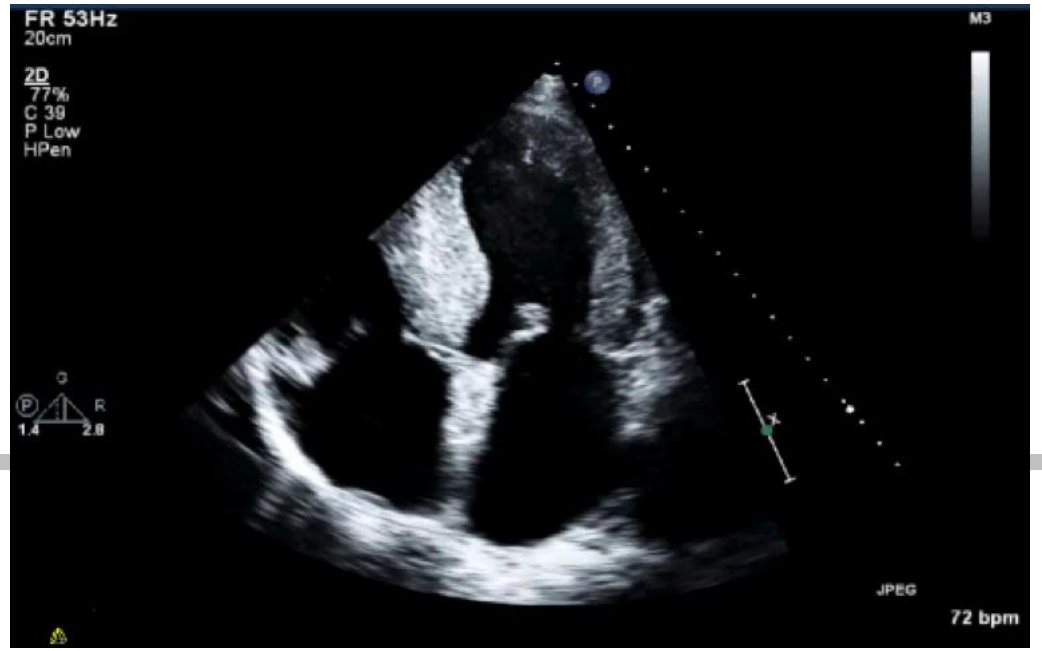
- Cardiac amyloidosis is highly prevalent and deadly, causing great morbidity and mortality to our society
- The field is exploding at an amazing pace given new diagnostic tools and the emergence of new therapies
- Opportunities for novel applications of therapies abound for a disease we're just starting to understand

Patient Case

- 53-year-old African American female
- Past medical history of hypertension and a family history of heart failure (father passed away in shock)
- Presented to clinic with worsening dyspnea with Zumba classes
- Found to in decompensated heart failure, admitted to our hospital for diuresis





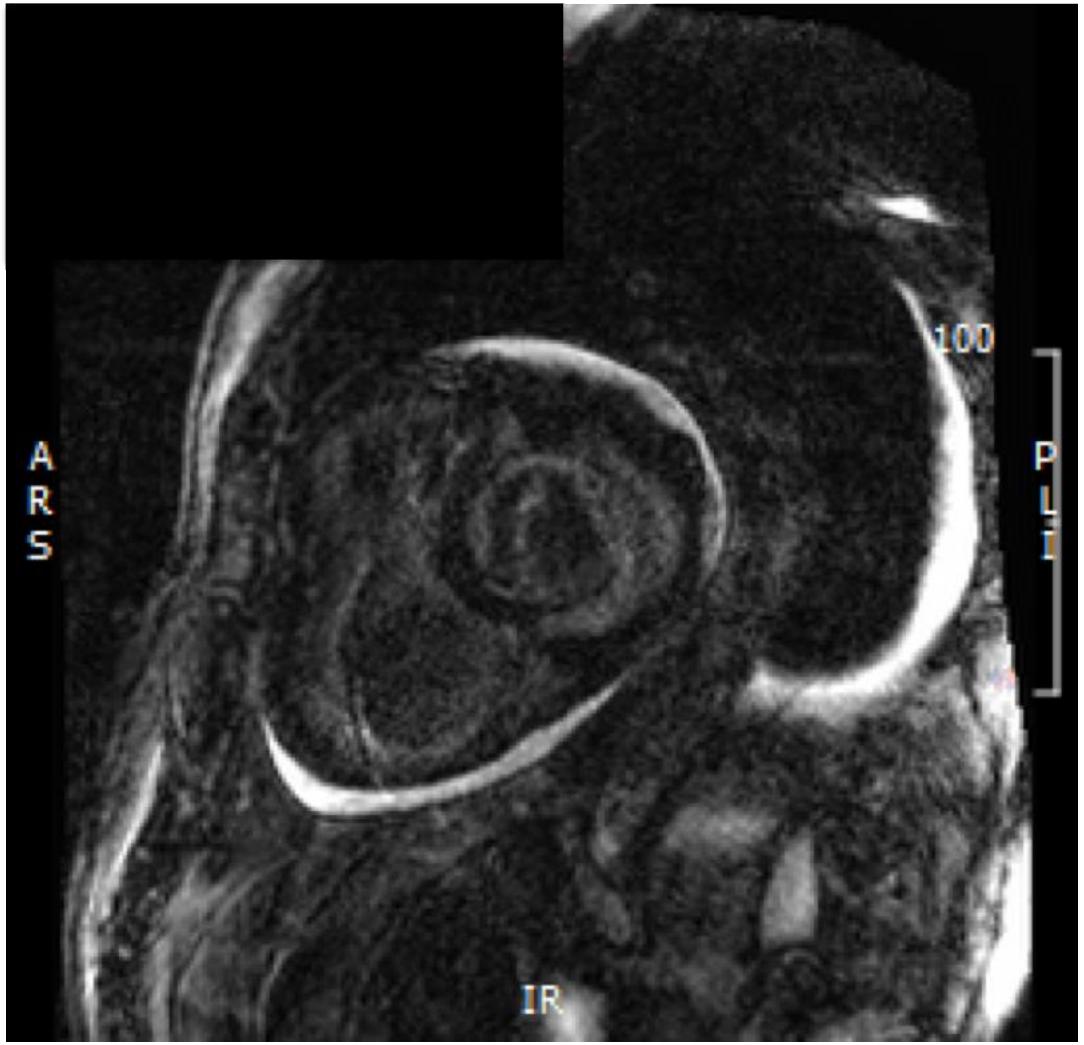


AT THE FOREFRONT
UChicago Medicine

Case

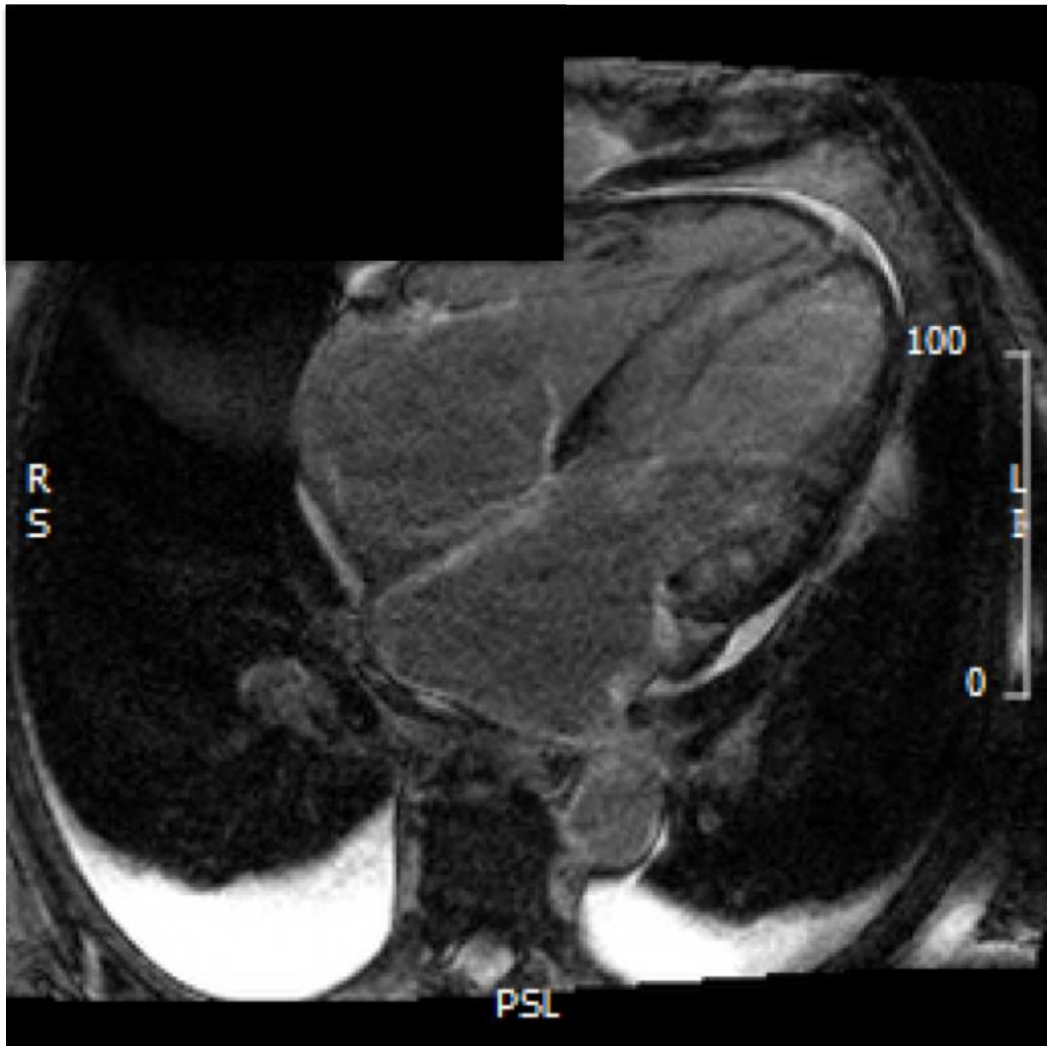
- Suspicion of infiltrative disease
- Admitted to history of carpal tunnel disease
- Sent for a cardiac MRI

Cardiac MRI



Diffuse subendocardial enhancement of LV and RV

Cardiac MRI



Diffuse enhancement in septum and subendocardium

Interatrial septum and atrial wall enhancement

Pleural effusions

Pericardial effusion

Case

- Suspicion of cardiac amyloidosis
- Lab work sent: SPEP, UPEP, light chains and all were normal
- PYP scan ordered and showed grade 3 uptake in the heart, no myocardial biopsy was performed

Case

- Felt to have likely TTR amyloidosis
- TTR genetic test sent
- Diuresed but had worsening renal function
- Right heart catheterization with restrictive filling pattern, diuresis guided by swan-ganz catheter
- Volume status stabilized, renal function improved

Case

- Followed closely in amyloidosis clinic and was found to have V122I mutation
- Currently on tafamidis and patisiran therapy
- Intracardiac pressures closely followed with CardioMems
- Able to resume her Zumba

What's Amazing About the Case

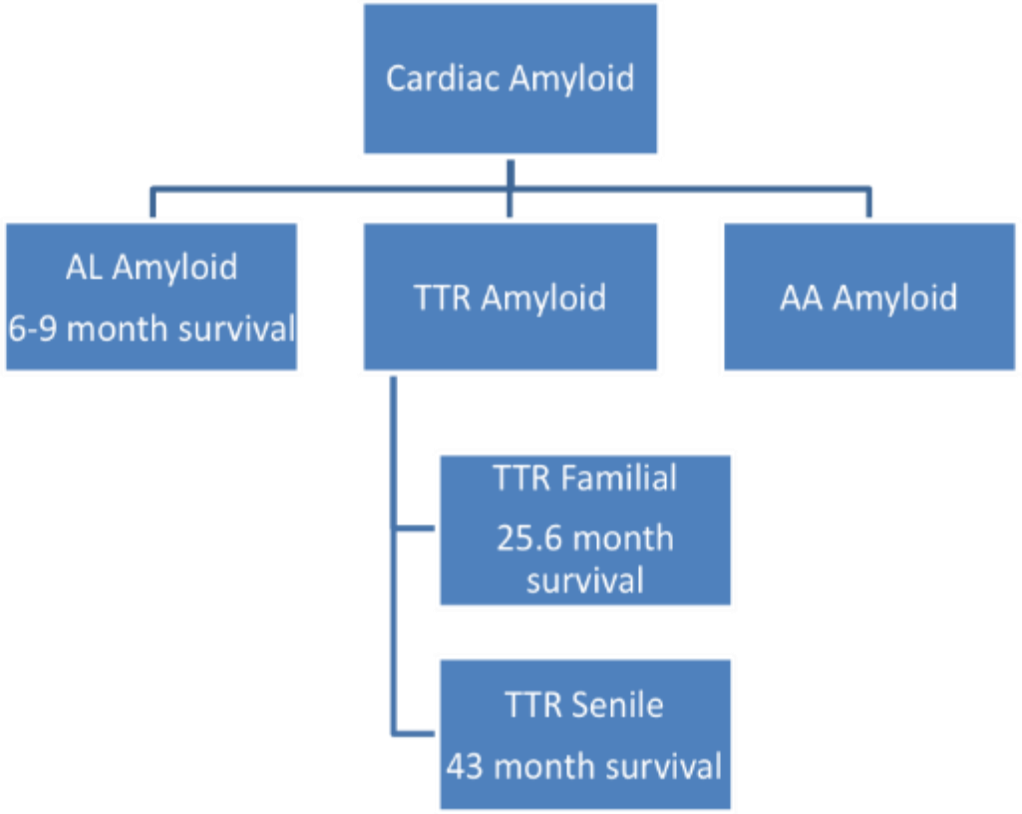
- The patient was able to turn around quickly and survive and to have a reasonable-quality of life once the disease was recognized and the hemodynamics understood

- A novel imaging technique in PYP allowed an essentially non-invasive diagnosis

- New therapies were able to be offered to "attack" the disease from multiple venues

Types of Cardiac Amyloidosis and Prognosis

A systemic disease that may present as a type of infiltrative cardiomyopathy



- hATTR is also known as TTR familial
- wtATTR is also known as senile

1. Grogan M, Dispenzieri A. Natural history and therapy of AL cardiac amyloidosis. Heart Fail Rev 2015; 20: 155-62
2. Grogan et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: TRACS. Am Heart J 2012 Aug; 164(2):222-228.

Hereditary TTR

Over 100 known mutations

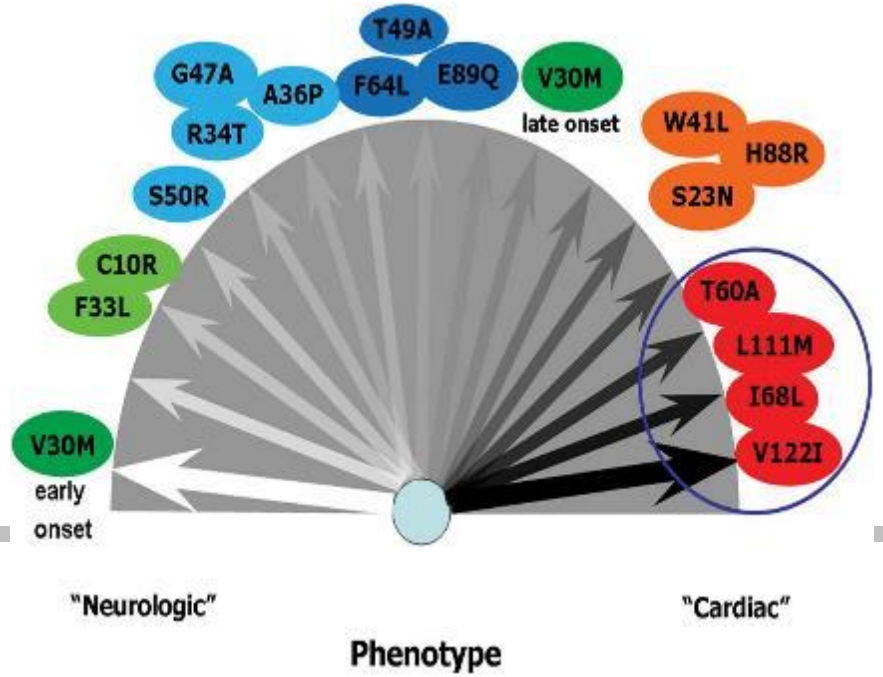
- 3 most common *TTR* mutations: Thr60Ala, Val30Met, Val122Ile

Patients with the Val122Ile variant are generally older and have a higher degree of cardiac infiltration than patients with the other two mutations

- 3.9% of African Americans and 23% of African Americans who have cardiac amyloidosis

Val30Met

- Most common mutation worldwide
- Neuropathy at presentation
- Development of cardiomyopathy later in the disease course

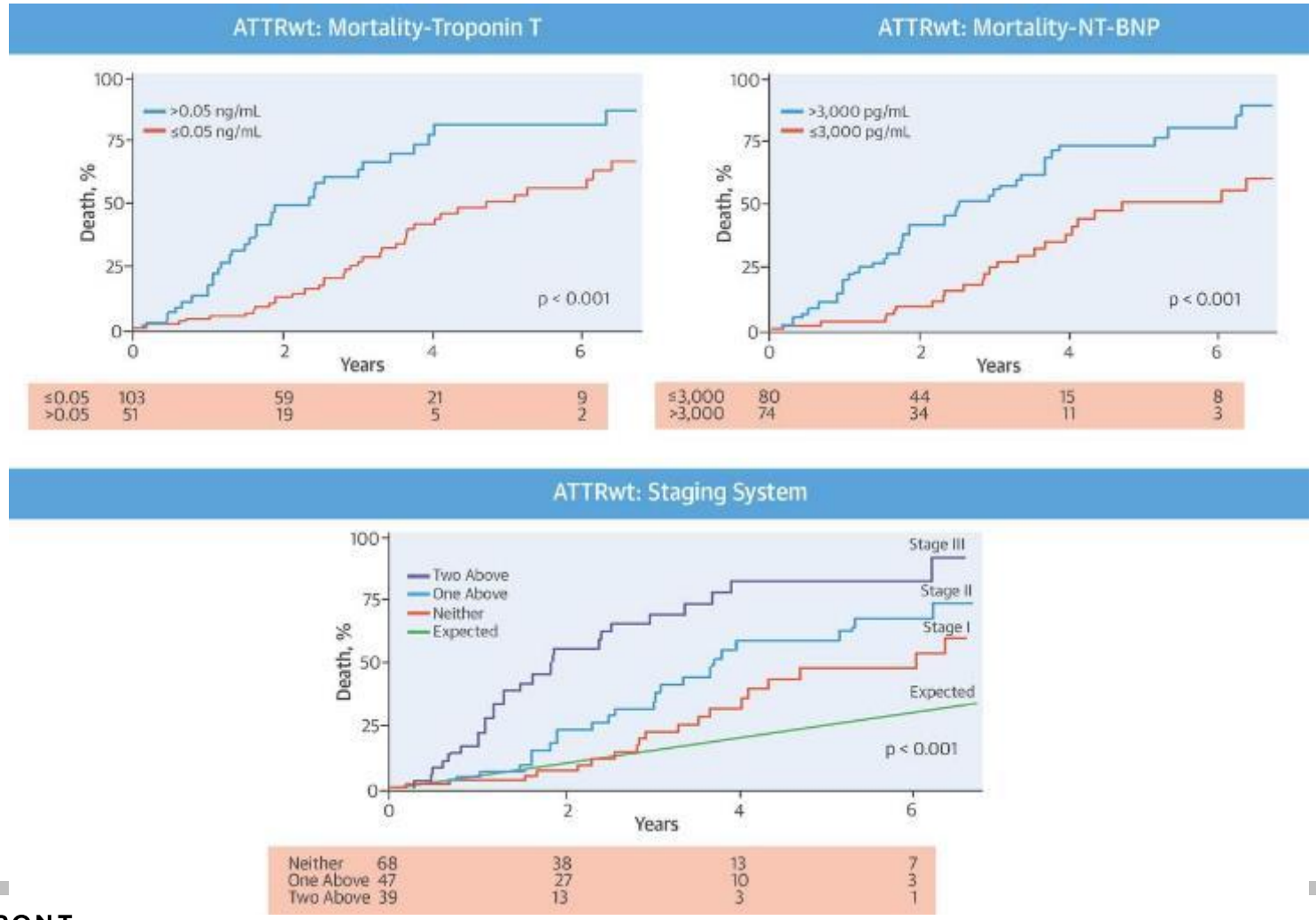


Rapezzi et al. European Heart Journal. 34 (7): 520-528

Wild Type TTR (formerly known as senile)

- Non-hereditary form
- Predominantly affects the heart + carpal tunnel, neuropathy is uncommon
- Can also present as spinal stenosis or biceps tendon rupture (often years before a cardiac presentation)
- Patients are usually >60 years old, male predominance
- May be a process of aging

Staging system: Mayo Clinic



Martha Grogan et al. JACC 2016;68:1014-1020

AT THE FOREFRONT
UChicago Medicine

JACC

A new staging system from the UK

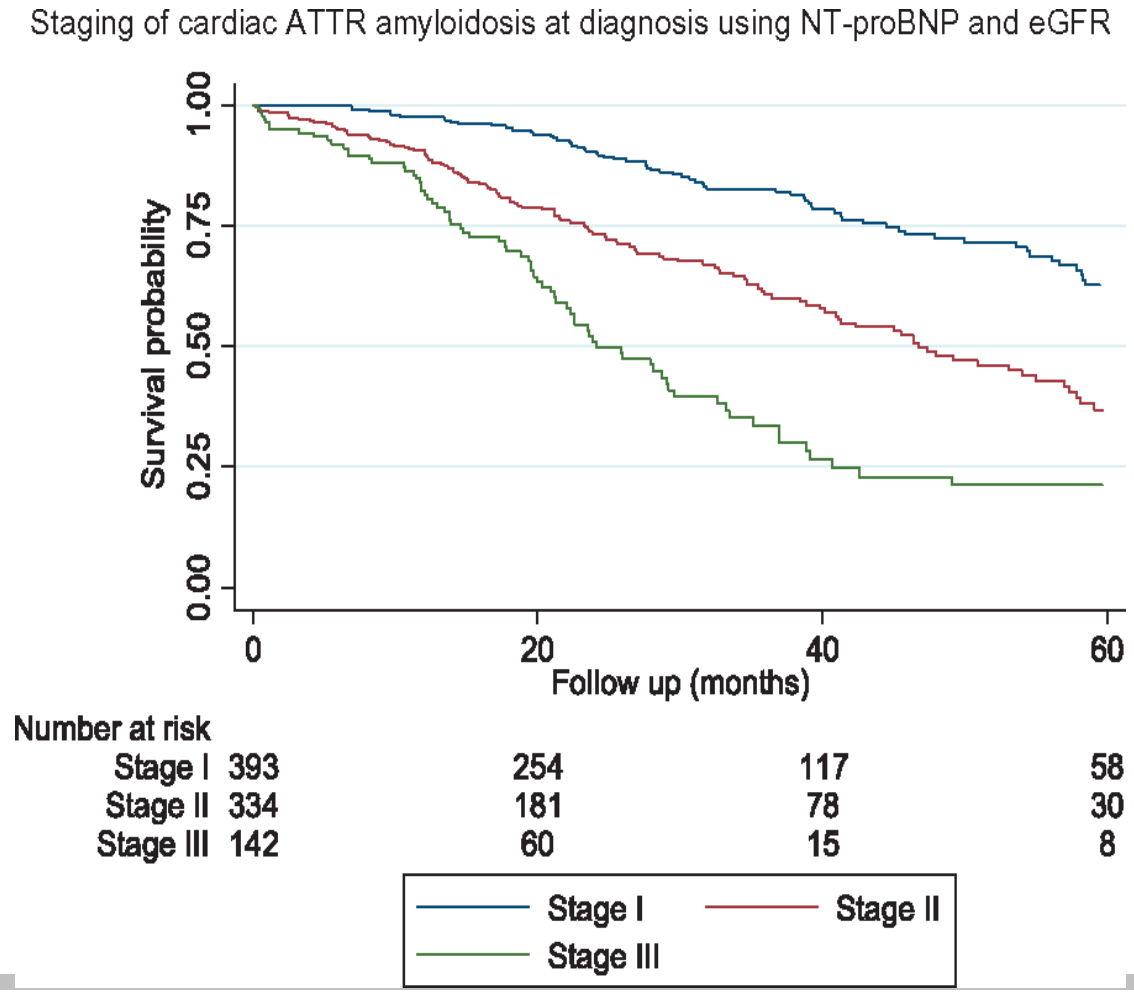
ESC European Society of Cardiology

Survival probabilities in 869 patients with cardiac transthyretin amyloidosis stratified by disease stage:

Stage I patients had a median survival of **69.2 months**

Stage II patients had a median survival of **46.7 months**

Stage III patients had a median survival of **24.1 months**



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Are TTR fibrils myo-toxic?

- In TTR amyloidosis: tetramer breaks down into monomers which misfold and produce oligomers
- Oligomers are deposited in tissues along with the mature amyloid fibrils, and oligomeric deposition has been shown, experimentally, to produce toxic apoptotic cell death
- still unclear whether oligomer deposition produces cardiac toxicity independent of the damage caused by the amyloid fibrils

AND/OR

Deposition of fibrils from either wild-type (ATTRwt) or mutated TTR (ATTRm) disrupt tissue architecture causing diastolic dysfunction, heart failure, eventual systolic dysfunction, and death

But amyloidosis is a rare disease, right?

Prevalence

- Autopsy study[1]:
  - 25% of patients >80 years old had TTR deposition
  - 2/3 of those had left ventricular involvement -> significant cardiac involvement in 8-16% of people >80 years old

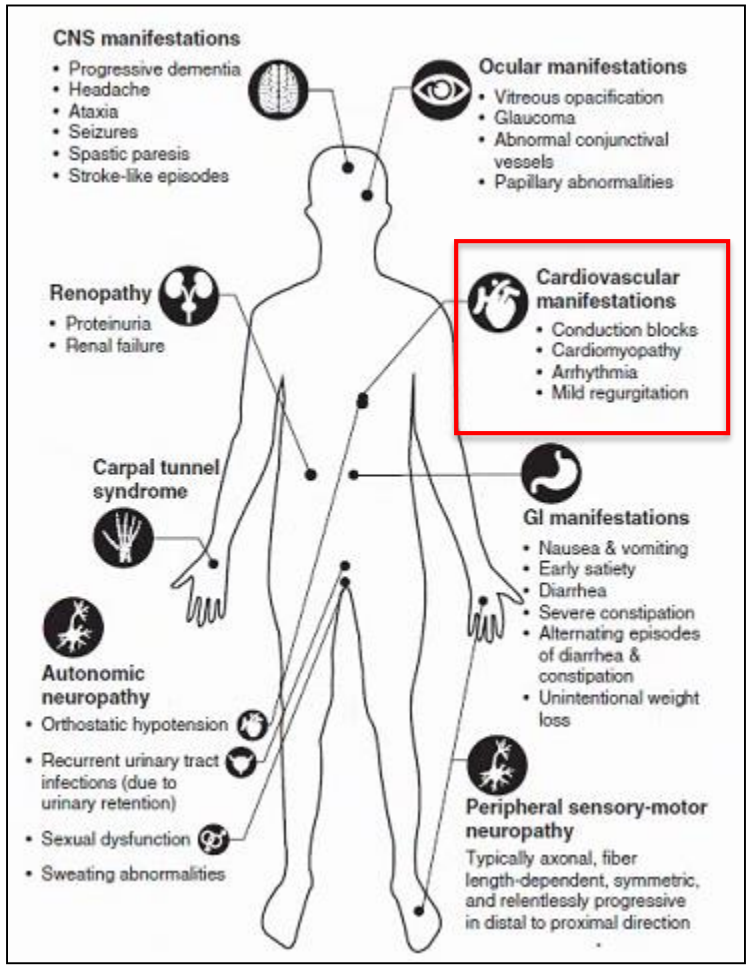
- Recent study of 151 patients undergoing TAVR for aortic stenosis: 16% of the patients[2] were PYP+

- Emerging data using nuclear scintigraphy has suggested that 13% (95% confidence interval, 7.2% -19.5%) of patients hospitalized with heart failure with preserved ejection fraction may have ATTRwt-CA[3] (wt-ATTR with cardiac involvement)

1. Cornwell et al. Am J Med. 1983;75:618-623.
2. Castano et al. Eur Heart J. 2017 Oct 7;38(38):2879-2887.
3. Gonzalez-Lopez et al. Eur Heart J. 2015 Oct 7;36(38):2585-94.

What are signs and symptoms of the disease?

Features Associated With hATTR Amyloidosis



RED-FLAG SYMPTOMS

Heart failure: +

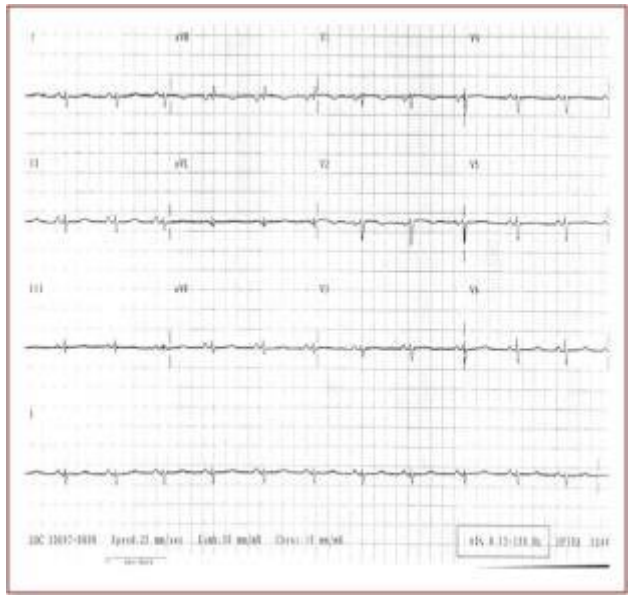
- Bilateral carpal tunnel syndrome
- Orthostatic hypotension
- GI problems: constipation or diarrhea

Conceicao; "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy; Journal of the Peripheral Nervous System 21:5–9 (2016)

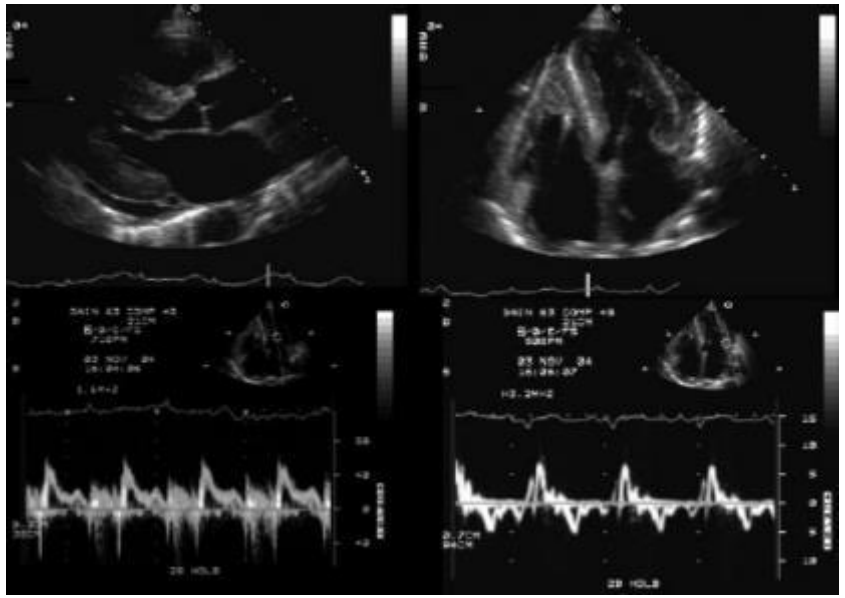
Disease symptoms are vague, but this disease is not very rare and is deadly.

How do cardiologists diagnose this disease?

Diagnostic Tools



- Low QRS voltage
  - prevalence of low voltage varies with etiology, ranging from 60% in AL to 20% in ATTR amyloidosis
- Poor R wave progression
- Right bundle-branch block is uncommon
- Left bundle-branch block is very unusual unless it is a preexisting condition



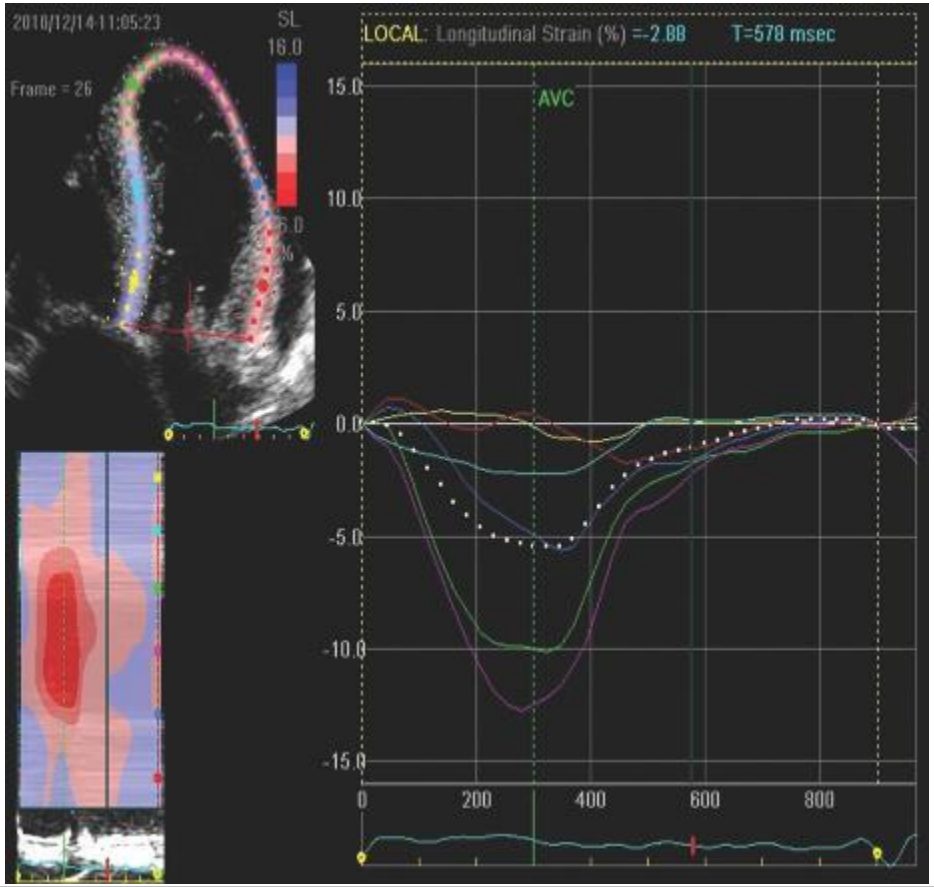
- LV and RV wall thickening
- bi-atrial enlargement
- thickening of the inter-atrial septum
- pericardial effusion
- diastolic dysfunction is common and often advanced restri ctive filling pattern
- high early (E) and relatively low atrial (A) wave with an E/ A ratio >2, and a short deceleration time
- myocardium may have a

"granular sparkling" or "speckled" appearance

Transthoracic Echocardiogram With Speckle Tracking

Red and yellow lines represent longitudinal motion in the basal segments, whereas the purple and green lines represent apical motion.

- Detects changes in regional myocardial deformation specific to amyloid
- Impairments in strain may occur earlier than can be seen in 2-D TTE or by symptoms
- Compared to other LVH
- Significantly reduced longitudinal and radial strain
- Diminished global longitudinal strain (LS) in base/mid segments, preserved at apex



AT THE FOREFRONT
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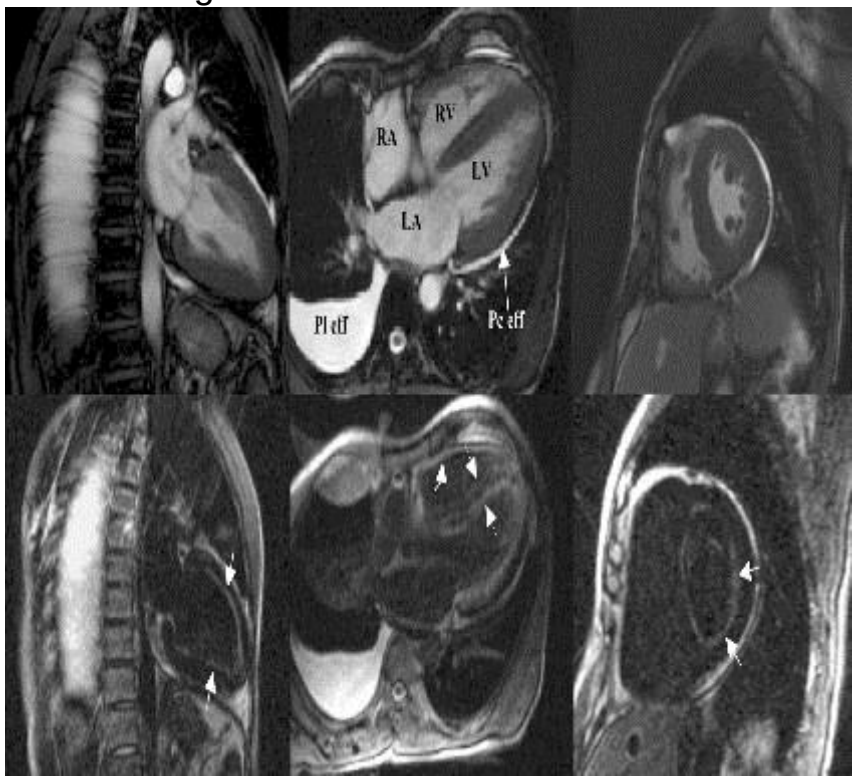
Sanjay M. Banypersad et al. J Am Heart Assoc 2012;1:e000364

Cardiac Magnetic Resonance (CMR) in a Patient With Systemic Amyloidosis

Top: Thickened LV, pleural and pericardial effusions
Bottom: Diffuse global subendocardial gadolinium enhancement



•Characteristic patterns of LGE: Global subendocardial and transmural enhancement

•T1 mapping can analyze changes in myocardial longitudinal relaxation
- help distinguish amyloid from HCM
- pre-contrast and post-contrast T1 data can be used together to calculate the ECV
- a measurement of interstitial expansion which is significantly elevated in patients with CA, due to interstitial amyloid deposition

•T2 mapping can represent myocardial edema
- higher in untreated AL amyloidosis compared with treated AL and ATTR amyloidosis
- predictor of prognosis in AL amyloidosis

•Meta-analysis of CMR: 85% sensitivity, 92% specificity

•Pre-contrast and post-contrast T1 data can be used together to calculate the ECV
ECV is a measurement of interstitial expansion which is significantly elevated in patients with CA, due to interstitial amyloid deposition

Alicia Maria Maceira et al. Circulation. 2005;111:186-193

Questions left to be answered

What is the best imaging modality to follow response to treatment?

What causes the LGE in cardiac amyloidosis?

Can MRI help us understand if TTR fibrils are toxic?

Which parameters are best for following treatment? T1/T2/ECV

Imaging With Nuclear Tracers

^{99m}Tc-DPD and PYP localizes cardiac amyloid deposits very sensitively

- Especially in patients with ATTR type
- Uptake of 99mTc-PYP occurs in about 1/3 of patients with cardiac AL amyloidosis
- Can help to distinguish AL from ATTR amyloidosis

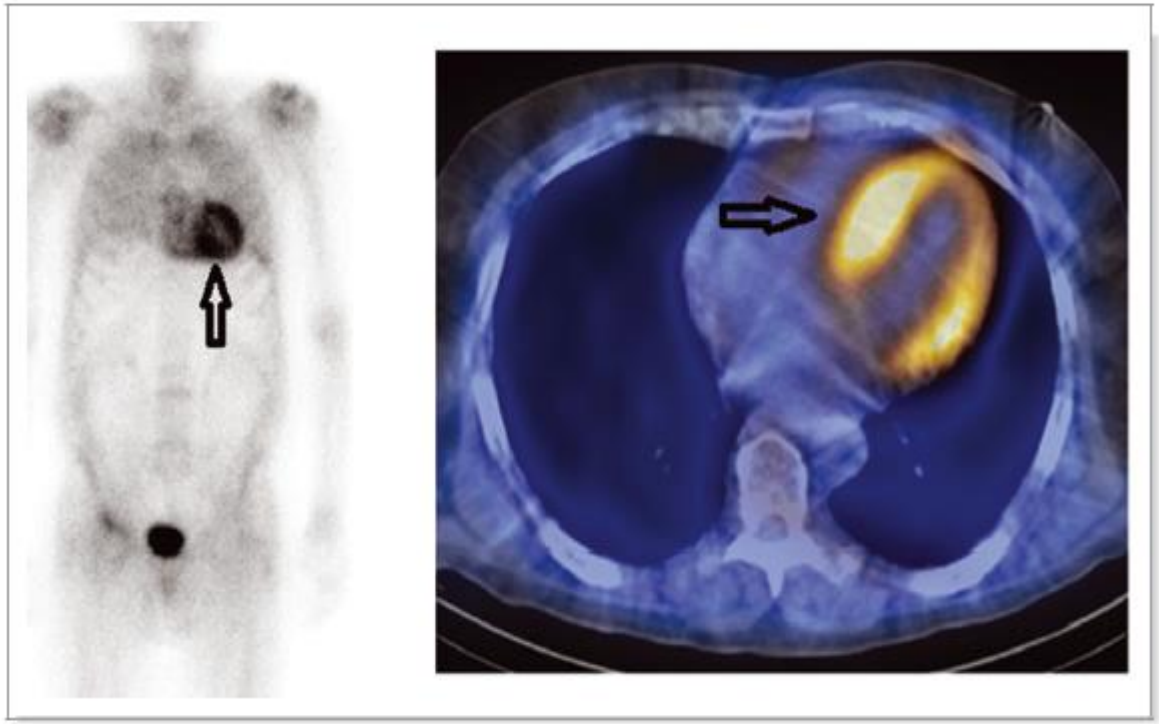


Figure 5. A positive 99mTc-DPD scan for TTR cardiac amyloid (left), showing uptake in the heart (arrow) and reduced bone uptake. The right-hand panel shows a fused CT/SPECT image showing myocardial uptake with greater uptake in the septum.

Asymptomatic cardiac ATTR deposits seen at an early stage when echocardiography, serum cardiac biomarkers, and perhaps even CMR remain normal

Imaging With Nuclear Tracers

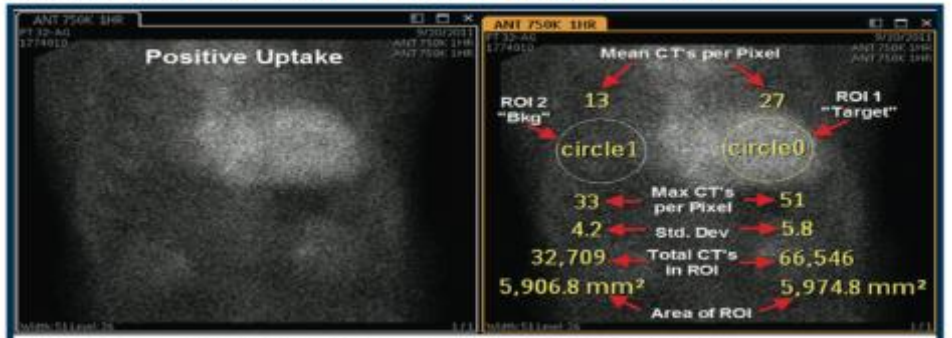
^{99m}Tc-PYP testing

- Can calculate a quantitative heart to contralateral lung ratio which correlates with prognosis
- Able to identify early-stage TTR-CM in asymptomatic carriers of variant transthyretin
- Able to diagnose TTR-CM without the complications that can arise with cardiac biopsy
- May be contributing to the increasing recognition of this disease

Table 2. Semi-quantitative Visual Grading of Myocardial ^{99m}Tc-PYP Uptake by Comparison to Bone(rib) Uptake

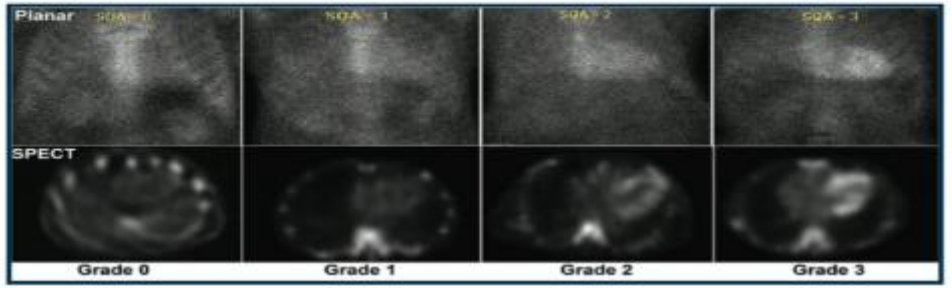
Grade	Myocardial ^{99m}Tc-PYP Uptake
Grade 0	no uptake and normal bone uptake
Grade 1	uptake less than rib uptake
Grade 2	uptake equal to rib uptake
Grade 3	uptake greater than rib uptake with mild/ absent rib uptake

Figure 1. Quantitation of Cardiac ^{99m}Tc-PYP Uptake Using Heart to Contralateral Lung (H/CL) Ratio



Biopsy proven ATTR with H/CL = 2.08

Figure 2. Grading ^{99m}Tc-PYP Uptake on Planar and SPECT Images



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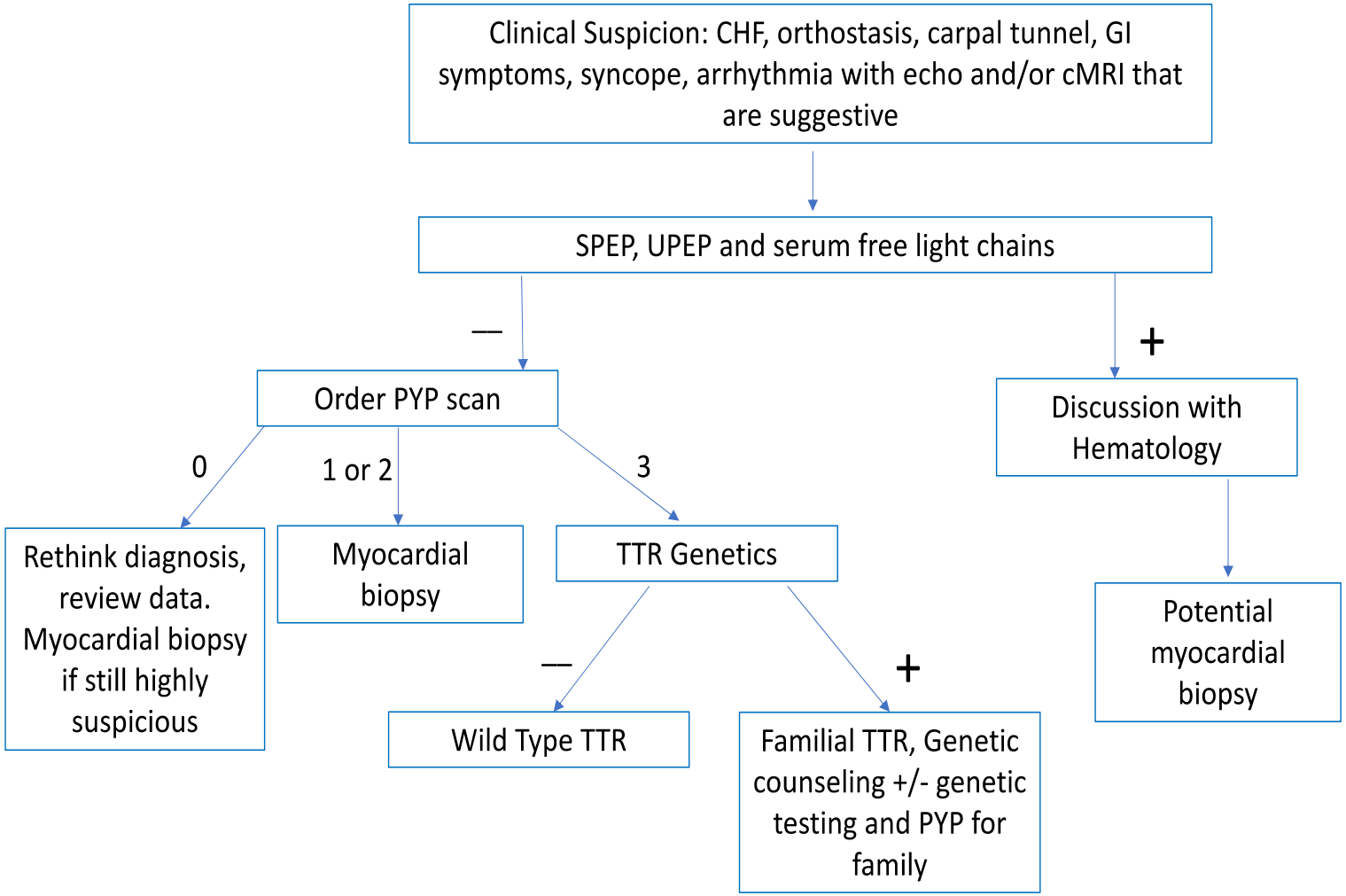
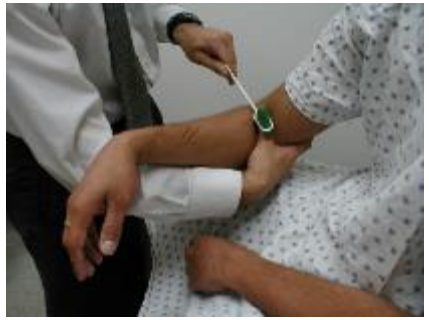
We now have a high suspicion that the patient has cardiac amyloidosis, so how do we figure out which type?

University of Chicago Diagnostic Algorithm
For Cardiac Amyloidosis



So now we know they have amyloid and what type, where do we go from here?

Treating ATTR Amyloidosis Requires a Multi-disciplinary Team



Neurologist

Genetic Counselor

Cardiologist

Hematologist

Gastroenterologist

AT THE FOREFRONT
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Advanced Heart Failure Treatment

- LVAD: rarely done given small LV cavity, multi-organ involvement, chance of reoccurrence of disease and risk of infection

- Heart Transplant: controversial for AL, more clear for TTR

  Current guidelines endorse consideration of selected patients with either AL or ATTR-CA.

Therapeutic Approaches: Approved

- Stabilize the TTR tetramer
  - Tafamidis
  - Diflunisal

- Prevent TTR production
  - Patisiran
  - Inotersen

Therapeutic Approaches: Trials

- Stabilize the TTR tetramer
  - Phase 3 trial: AG10

- Prevent TTR production
  - Phase 3 trial: APOLLO-B – evaluate Patisiran in TTR cardiomyopathy
  - Phase 3 trial: HELIOS-B – evaluate Vutrisiran in TTR cardiomyopathy
  - Phase 3 trial: Cardio-TTRansform – evaluate Akcea-TTR-LRx in TTR cardiomyopathy

- Breakdown TTR protein
  - Doxycycline + TUDCA

Whom to Treat?

Any symptomatic patient

- HF requiring diuretics, hospitalization, dyspnea
- Neurological impairment

Asymptomatic but PYP grade 2 or 3 with a known mutation

Phenotype:

- Cardiac -> tafamidis
- Mixed -> patisiran and tafamidis[1]
    - inotersen and tafamidis[1]
- Neurologic: patisiran or inotersen

1. There have been no clinical trials conducted to formally evaluate the concomitant use of patisiran and tafamidis, or inotersen and tafamidis

Conclusions

TTR cardiac amyloidosis is a prevalent, deadly, underdiagnosed disease in our patient population

New nuclear imaging techniques allow less invasive diagnostics

Therapeutic options remain limited but hopeful new treatments in development

Data Gaps

1. Natural history of ATTR
   Timing of PYP -> cMRI -> biopsy?
2. Women in ATTR
3. True prevalence of wild type TTR
4. Is wide-spread screening in high risk populations cost effective?
5. What is the prognosis of ATTR in the modern era with new treatments?
6. What do we do with PYP grade 1?
7. Can cMRI predict arrhythmic burden?
8. Can cardiomems decrease hospitalizations for patient with ATTR?
9. Layering of therapies
10. Efficacy of siRNAs with wild type
11. Tailoring of therapies to mutation

Transthyretin (TTR) Amyloidosis

ONPATTRO (patisiran) and Vutrisiran

ONPATTRO Program Update

- Eric Green, SVP & General Manager, TTR Program

Cardiac Amyloidosis: A New Paradigm

- Nitasha Sarswat, M.D., Director, Infiltrative Cardiomyopathy Program
  University of Chicago Medicine

Expanding the ATTR Opportunity

- Pushkal Garg, M.D., Chief Medical Officer

Continued Development

Potential for Expansion of TTR Franchise

- ONPATTRO approved for the polyneuropathy of hATTR amyloidosis (with or without cardiomyopathy) in adults
- Studies underway to evaluate patisiran and vutrisiran for ATTR amyloidosis with cardiomyopathy
- Published clinical data support clinical hypotheses for potential expansion and have informed design of ongoing studies

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.

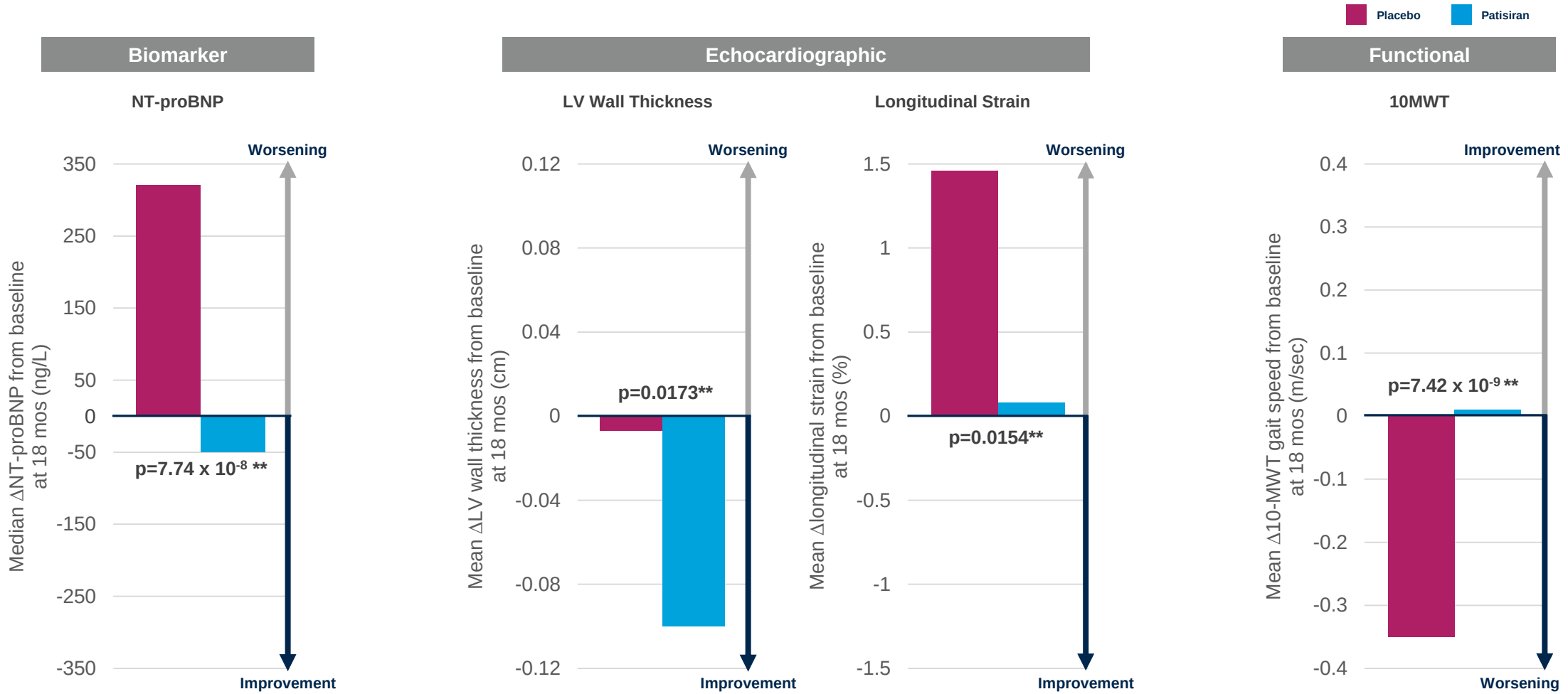
99% of patients who completed APOLLO study enrolled in Global OLE study

OLE, open-label extension; ClinicalTrials.gov Identifier: NCT02510261

Adams D, et al. BMC Neurology 2017

Exploratory Cardiac Endpoints in APOLLO

Support Further Clinical Development in ATTR-CM



Solomon S, et al, Circulation 2018

* 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

Cardiac Safety Profile in APOLLO

Support Further Clinical Development in ATTR-CM

	Placebo (n=77)	Patisiran (n=148)
Total duration of exposure, years	96.1	218.9
Cardiac AEs, n (%)	28 (36.4)	42 (28.4)
Cardiac serious AEs, 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	5 (3.4)
Torsades des pointes SMQ AEs, n (%)†	14 (18.2)	8 (5.4)
Cardiac failure SMQ AEs, n (%)	8 (10.4)	14 (9.5)

AE, adverse event; CI, confidence interval; HLGT, high-level group term; HLT, high-level term; HR, hazard ratio; SMQ, standard MedDRA query.

*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.

†The Torsades de pointes SMQ is a search for events that may be associated with Torsades de pointes. It does not mean that these are confirmed events of Torsades de pointes. No events of Torsades de pointes have been reported.

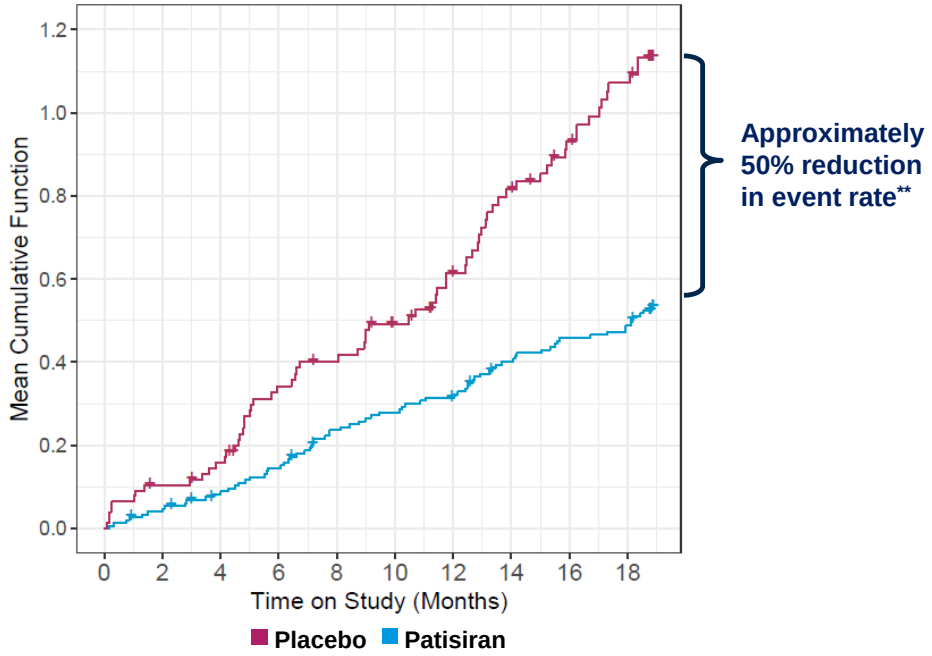
Solomon et al. Circulation 2018

Post Hoc Analysis of Mortality & Hospitalization in APOLLO

Support Further Clinical Development in ATTR-CM

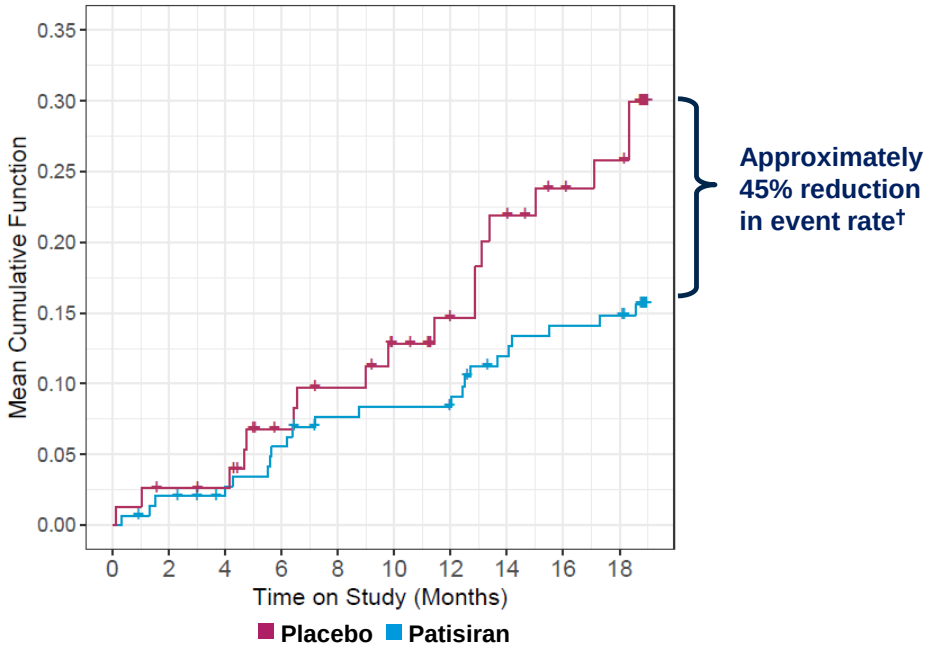
Mean Cumulative Function: average number of events per patient by a certain time

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

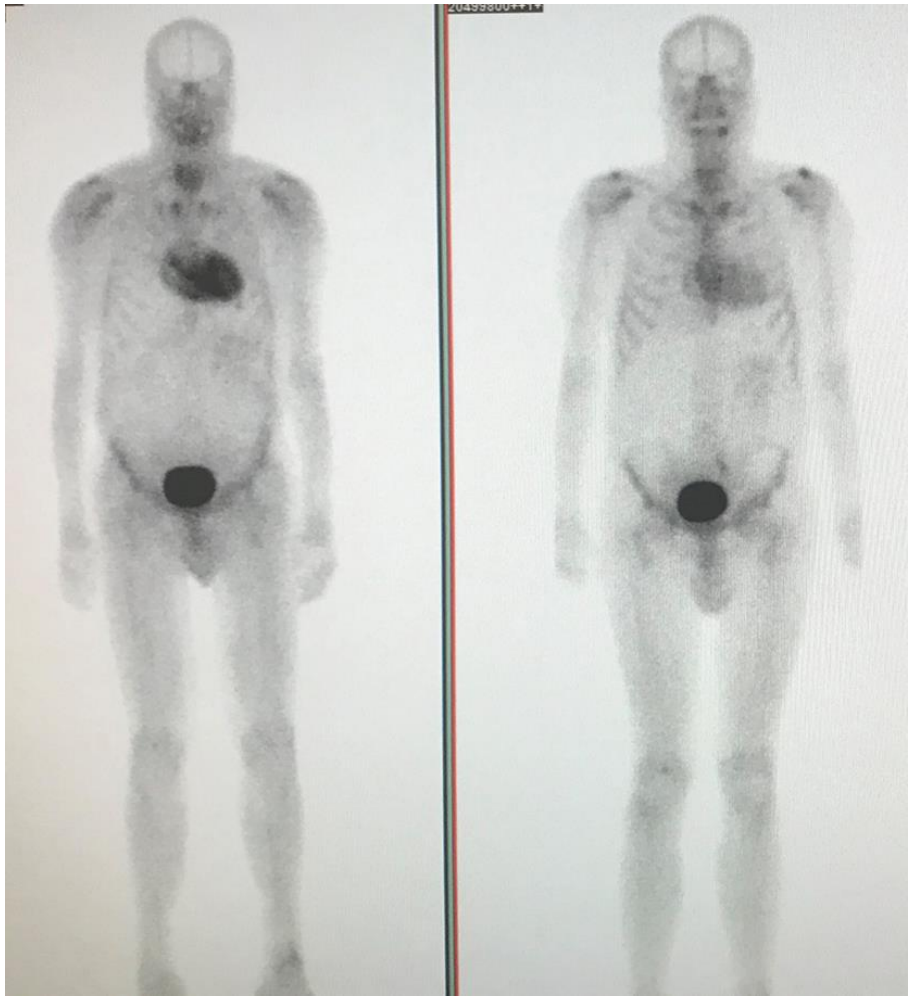
Changes in Cardiac Imaging Observed After Patisiran Treatment of hATTR Amyloidosis

- Data from recent uncontrolled case series* suggests patisiran treatment may halt or reverse aspects of ATTR-CM

- Serial images from one patient show reduced DPD uptake after patisiran treatment
  - ~60 y.o. man with V30M mutation enrolled in Expanded Access Program
  - Mixed phenotype; polyneuropathy predominant
  - Initiated patisiran (on top of ongoing diflunisal) due to disease progression

- Raises hypothesis that patisiran treatment may be associated with cardiac remodeling and/or amyloid regression

- Cardiac effects to be further assessed in randomized, controlled trials



Baseline 12 Months

* Gilmore, OTS Munich 2019

Patisiran APOLLO-B Phase 3 Study*

Randomized, Double-Blind, Placebo-Controlled Study in ATTR Amyloidosis Patients with Cardiomyopathy

N ~ 300
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
  - TTR stabilizer naïve and/or TTR stabilizer progressor
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤III; minimum walk and NT-proBNP limits at baseline

1:1 RANDOMIZATION

Patisiran
IV q3w†
0.3 mg/kg

or

Placebo
IV q3w†

Primary Endpoint

- Change in 6-MWT at 12 months

Key Secondary Endpoints

- Cardiomyopathy symptoms and health status
- Death and hospitalization outcomes
- Cardiac biomarkers

12-Month Treatment Extension

ClinicalTrials.gov Identifier: NCT03997383

APOLLO-B

Study initiated
September 2019

Results expected 2021/2022

*Concomitant use of local standard of care allowed during study, including TTR stabilizer
† To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min. before each study drug infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers
NYHA: New York Heart Association; NT-proBNP: N-terminal pro b-type natriuretic peptide; 6-MWD: 6-Minute Walk Distance

Cece
Living with hATTR Amyloidosis

Vutrisiran (previously ALN-TTRsc02)

Investigational RNAi Therapeutic

Follow-on RNAi therapeutic also targeting mutant and wild-type TTR

- Utilizes enhanced stabilization chemistry and GalNAc ligand to target liver delivery
- Administered as low volume subcutaneous injection once every 3 months

Completed Phase 1 study in healthy volunteers

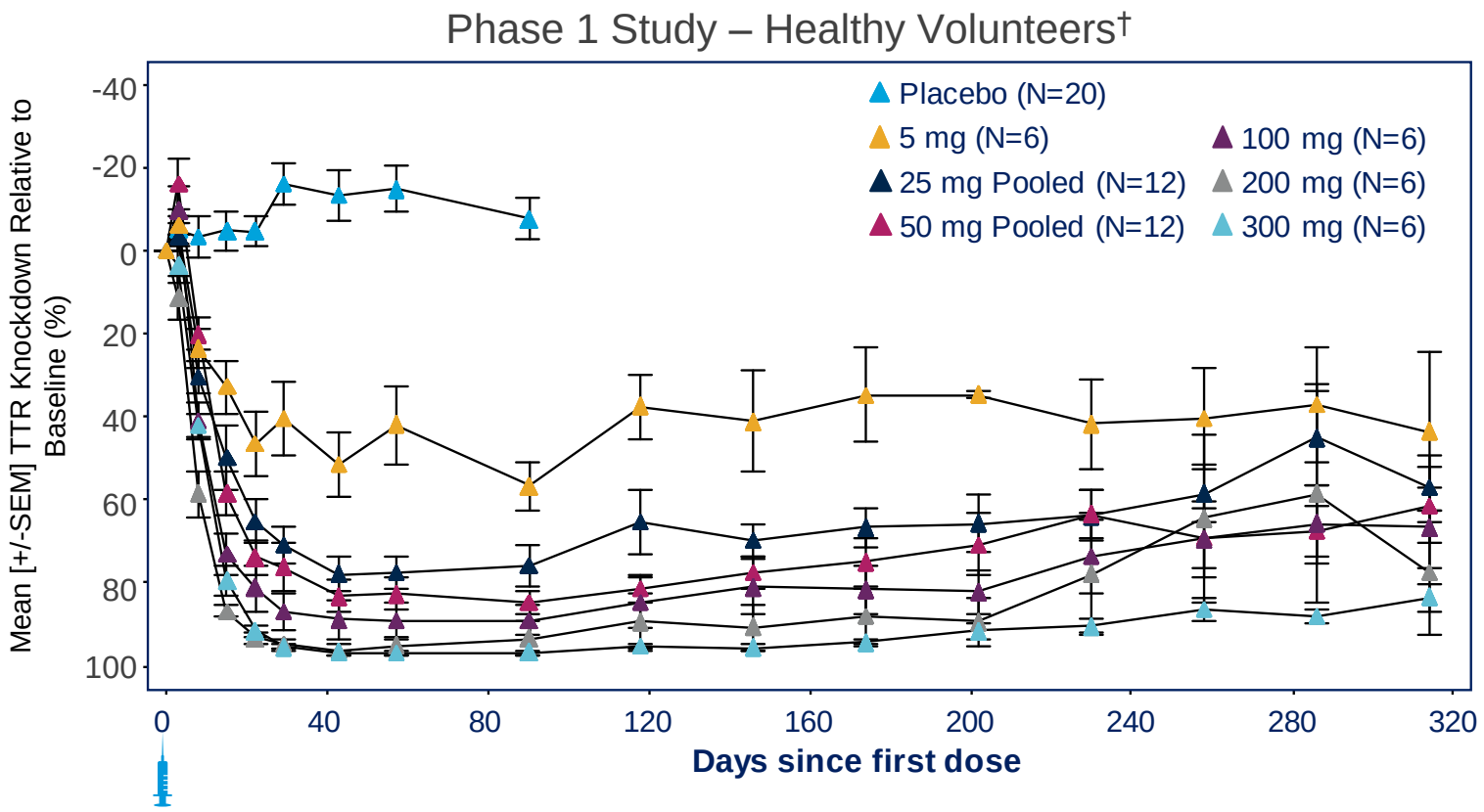
Robust HELIOS Clinical Development Program

- HELIOS·A study in hATTR amyloidosis initiated
- HELIOS·B study in ATTR amyloidosis initiated

Vutrisiran Opportunity

Advancing Continued Innovation to Patients with ATTR Amyloidosis

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



Vutrisiran

4 DOSES PER YEAR

~90% peak TTR KD predicted after repeat dosing

Safety (N=80):

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

† 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)

Vutrisiran HELIOS·A Phase 3 Study

Randomized, Open-Label Study in Hereditary ATTR Amyloidosis Patients

ClinicalTrials.gov Identifier: NCT03759379

HELIOS·A

Efficacy Assessments vs. APOLLO placebo arm

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

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

HELIOS-A Phase 3 study
now enrolling

Results expected 2021

^ Primary endpoint for the study is at 9 months
* ATTR amyloidosis – wild-type or any TTR mutation

Vutrisiran HELIOS·B Phase 3 Study

Randomized, Double-Blind Outcomes Study in ATTR Amyloidosis Patients with Cardiomyopathy

N ~ 600
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
  - ≤ 30% tafamidis use at baseline
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤ III; minimum walk and NT-proBNP limits at baseline

ClinicalTrials.gov Identifier: NCT04153149

1:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Primary Endpoint

- Composite outcome of all-cause mortality and recurrent CV hospitalizations (when last patient reaches Month 30)

Secondary Endpoints

- 6-MWT distance
- Kansas City Cardiomyopathy Questionnaire (KCCQ OS) score
- Mean left ventricular (LV) wall thickness
- Global longitudinal strain
- Composite of all-cause mortality and recurrent all-cause hospitalizations
- All-cause mortality
- Recurrent CV hospitalizations
- NT-proBNP

HELIOS·B

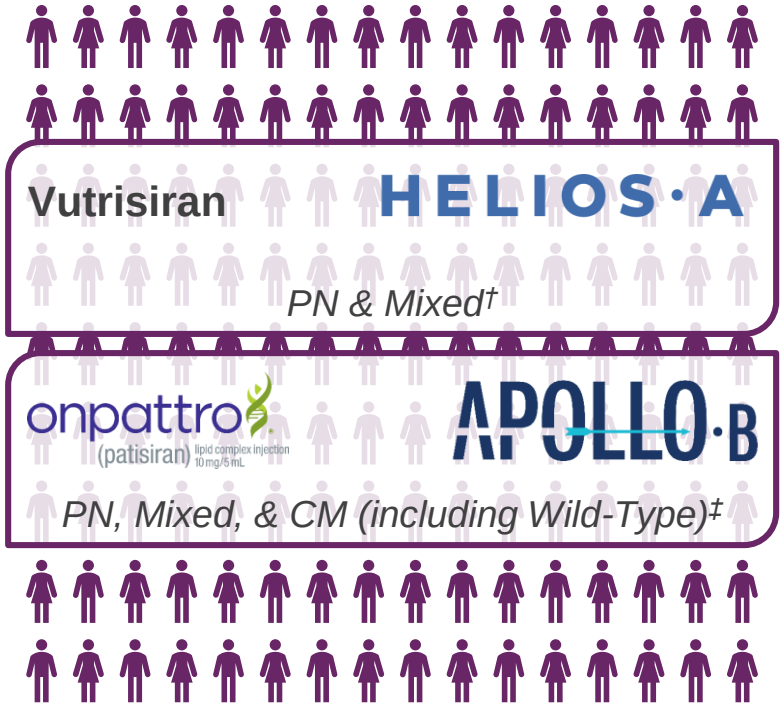
HELIOS-B **now initiated**

Study includes optional interim analysis

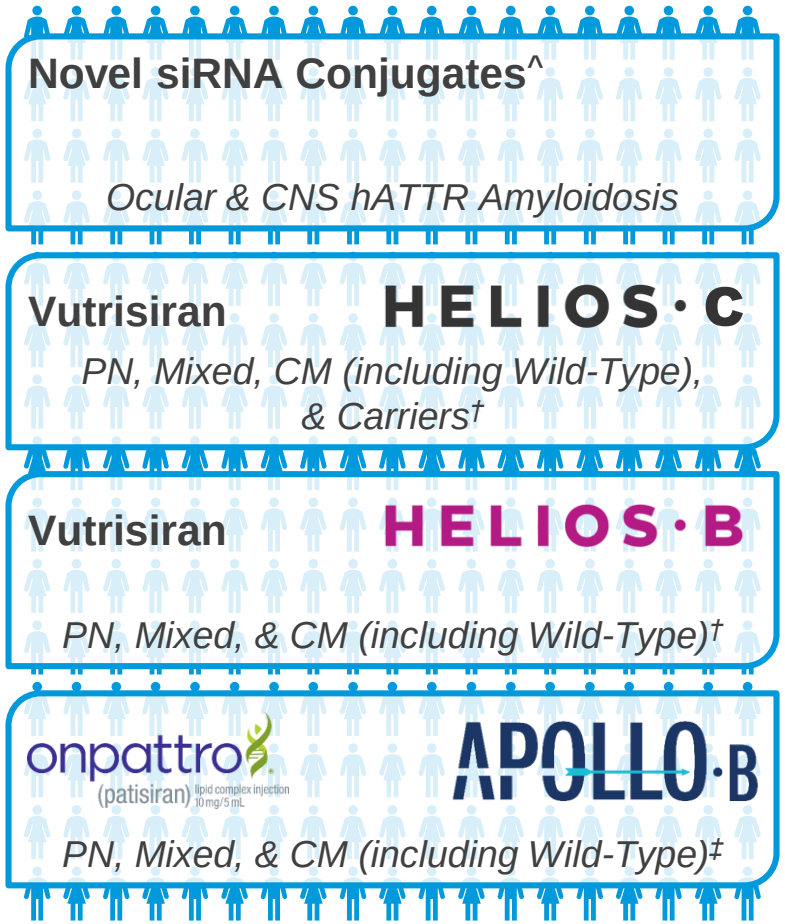
Alnylam ATTR Amyloidosis Franchise

Potential to Expand Value to Patients Globally for Many Years to Come

2019 – 2021



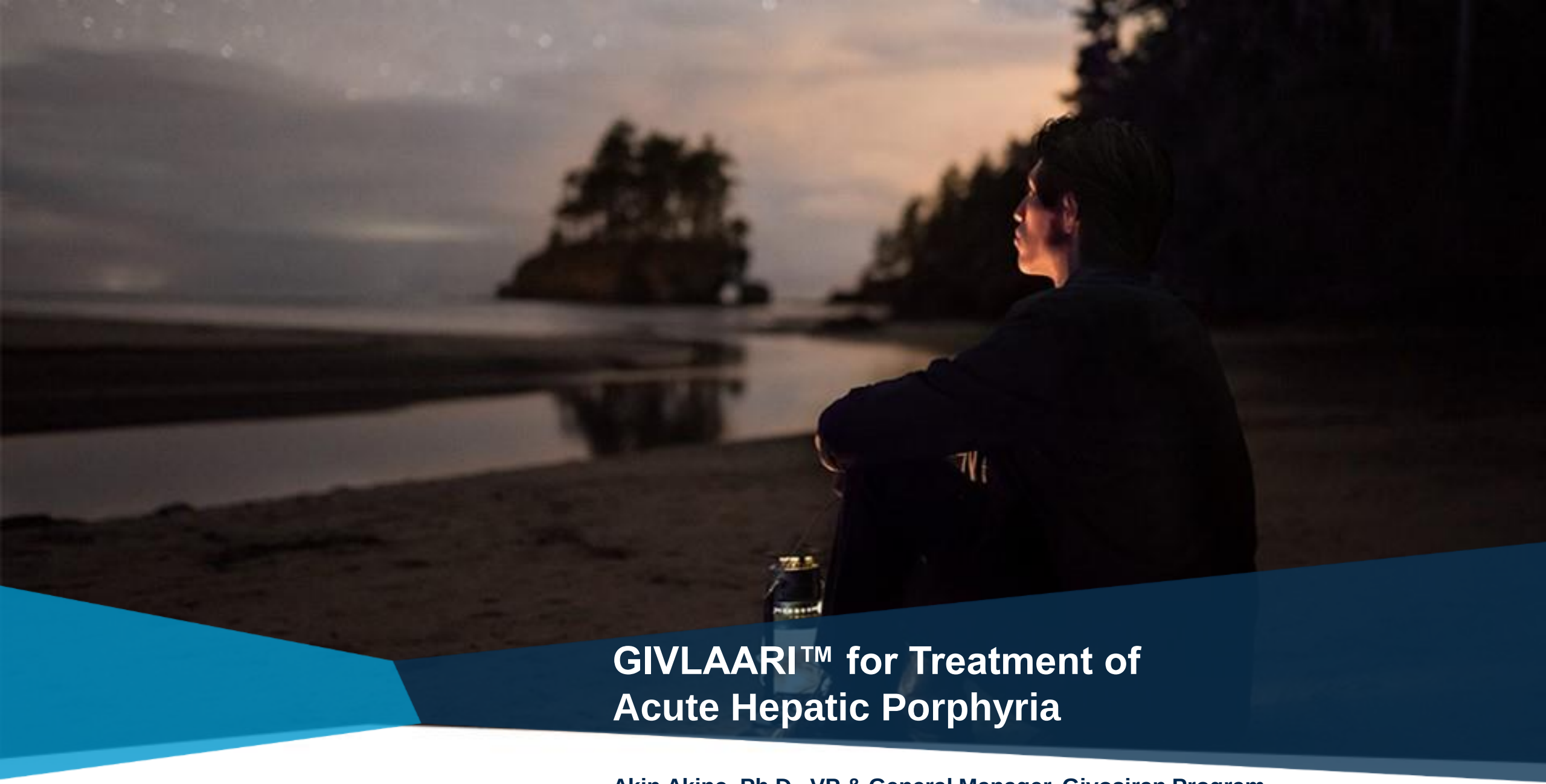
2021 – 2023



2023 & Beyond

* ONPATTRO is approved in the U.S. and Canada for the treatment of the polyneuropathy of hATTR amyloidosis in adults, in the EU and Switzerland for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; ‡ 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 is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; additional studies and future development possible; ^ Novel siRNA conjugate development candidates for ocular or CNS hATTR amyloidosis not yet selected.

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



GIVLAARI™ for Treatment of Acute Hepatic Porphyria

Akin Akinc, Ph.D., VP & General Manager, Givosiran Program
Andy Orth, SVP, Head of U.S. Business

Alnylam® PHARMACEUTICALS

Acute Hepatic Porphyria

GIVLAARI™ (givosiran)

Program Overview

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

Commercial Plans

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

Acute Hepatic Porphyria (AHP)

Family of Rare Genetic Diseases with Significant Disease Burden

Description

Causes potentially life-threatening attacks and chronic manifestations that negatively impact quality of life

Predominantly

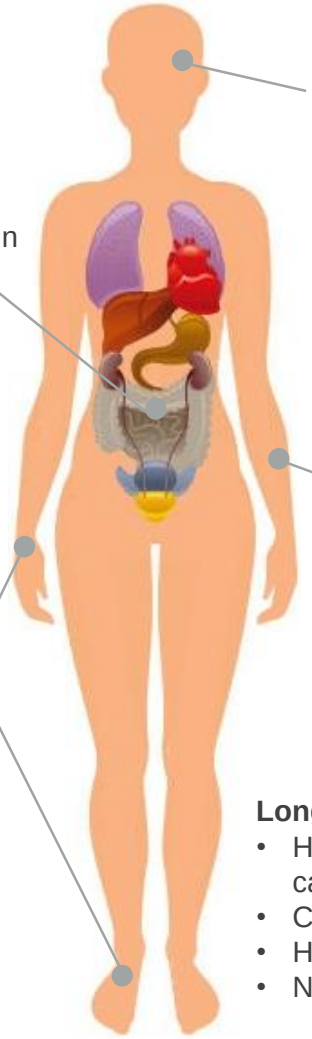
female

commonly misdiagnosed

Patient Population

~3,000

diagnosed in U.S./EU with active disease[1,2]



Autonomic Nervous System
- Severe abdominal pain
- Nausea/vomiting
- Hypertension
- Tachycardia
- Constipation
- Hyponatremia

Central Nervous System
- Confusion
- Anxiety
- Depression
- Memory loss
- Fatigue
- Hallucinations
- Seizures

Cutaneous†
- Lesions on sun-exposed skin

Peripheral Nervous System
- Neuropathic pain
- Sensory loss
- Muscle weakness
- Paralysis
- Respiratory failure

Long-term Complications
- Hepatocellular carcinoma
- Chronic kidney disease
- Hypertension
- Neuropathy

1. Elder et al. J Inherit Metab Dis 2013;36:849–57; 2. Data on file, IBM MarketScan Commercial Claims and Medicare Supplemental Database
† Symptoms specific to hereditary coproprophyria and variegate porphyria

Acute Hepatic Porphyria

Disease Overview[1,2]

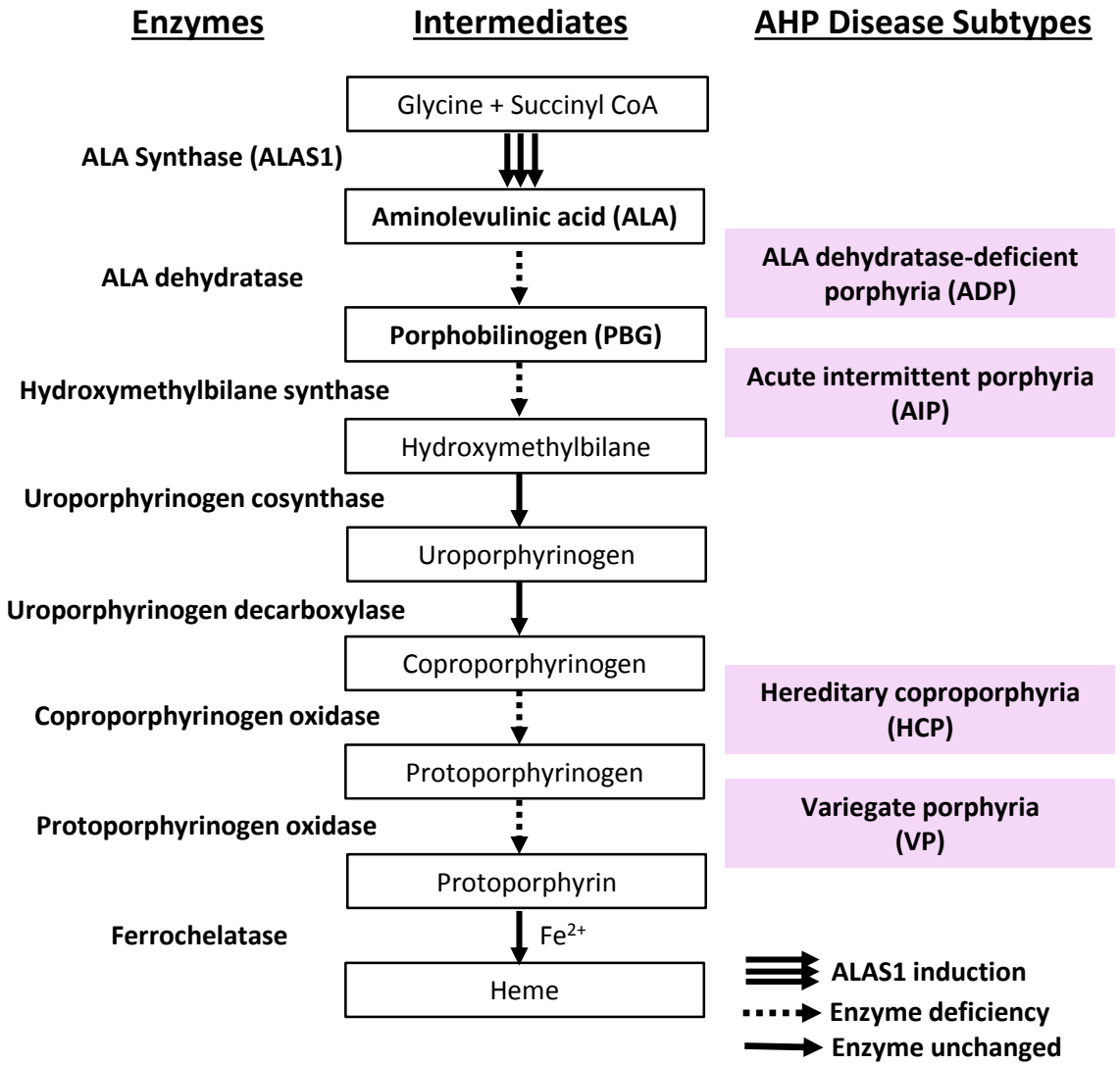
- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in the liver
- Acute Intermittent Porphyria (AIP) most common, with mutation in hydroxymethylbilane synthase (HMBS)

Disease Pathophysiology

- Induction of ALAS1 leads to accumulation of neurotoxic heme intermediates ALA/PBG
- ALA believed to be primary neurotoxic intermediate that causes disease manifestations

Attacks, Chronic Manifestations, and Comorbidities[3-7]

- Acute neurovisceral attacks can be life-threatening
- Chronic pain, fatigue, nausea, and anxiety
- Hypertension, chronic kidney disease and liver disease
- Disability and social isolation common among those with attacks



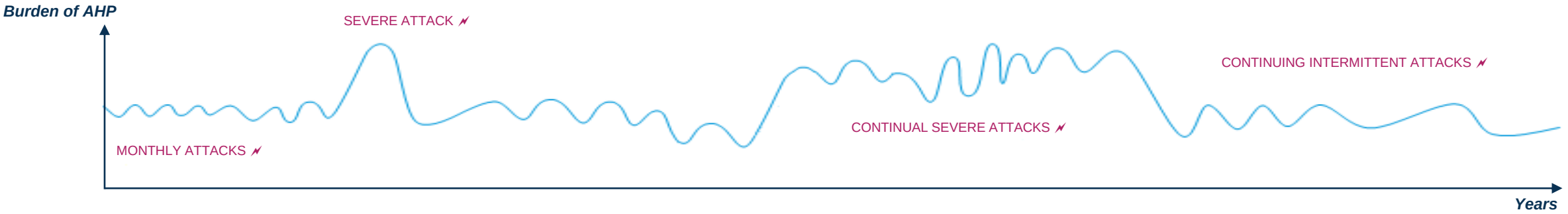
1. Bonkovsky, et al., Am J Med. 2014;127:1233-41; 2. Elder, et al., JIMD. 2013;36:849-57; 3 Pischik and Kauppinen. Appl Clin Genet. 2015;8:201-14. 4. Bonkovsky, et al., Poster. Presented at the American Association for the Study of Liver Diseases; November 9-13, 2018, San Francisco, CA, USA. 5. Stewart. J Clin Pathol. 2012;65:976-80. 6. Simon, et al., Patient. 2018;11:527-37. 7. Naik, et al., Mol Genet Metab. 2016;119:278-83.

Acute Hepatic Porphyria

Unpredictable Nature of AHP Places Burden on Patients

- Patients are frequently misdiagnosed (e.g., non-specific abdominal pain, fibromyalgia, depression, endometriosis) and undergo potentially unnecessary surgeries (e.g., cholecystectomy, appendectomy, hysterectomy)[1,2,5]
- Frequent healthcare utilization, reduced quality of life, and reduced employment all contribute to disease burden[3,4]
- Unpredictable nature of attacks is a source of fear and anxiety for patients

Illustrative Patient Experience with AHP



- In the words of patients

> "The pain is all consuming. I mean it's like someone is holding, squeezing, stabbing. You're not able to function. You can't do anything, you just want to die..."
>
> -AHP Patient

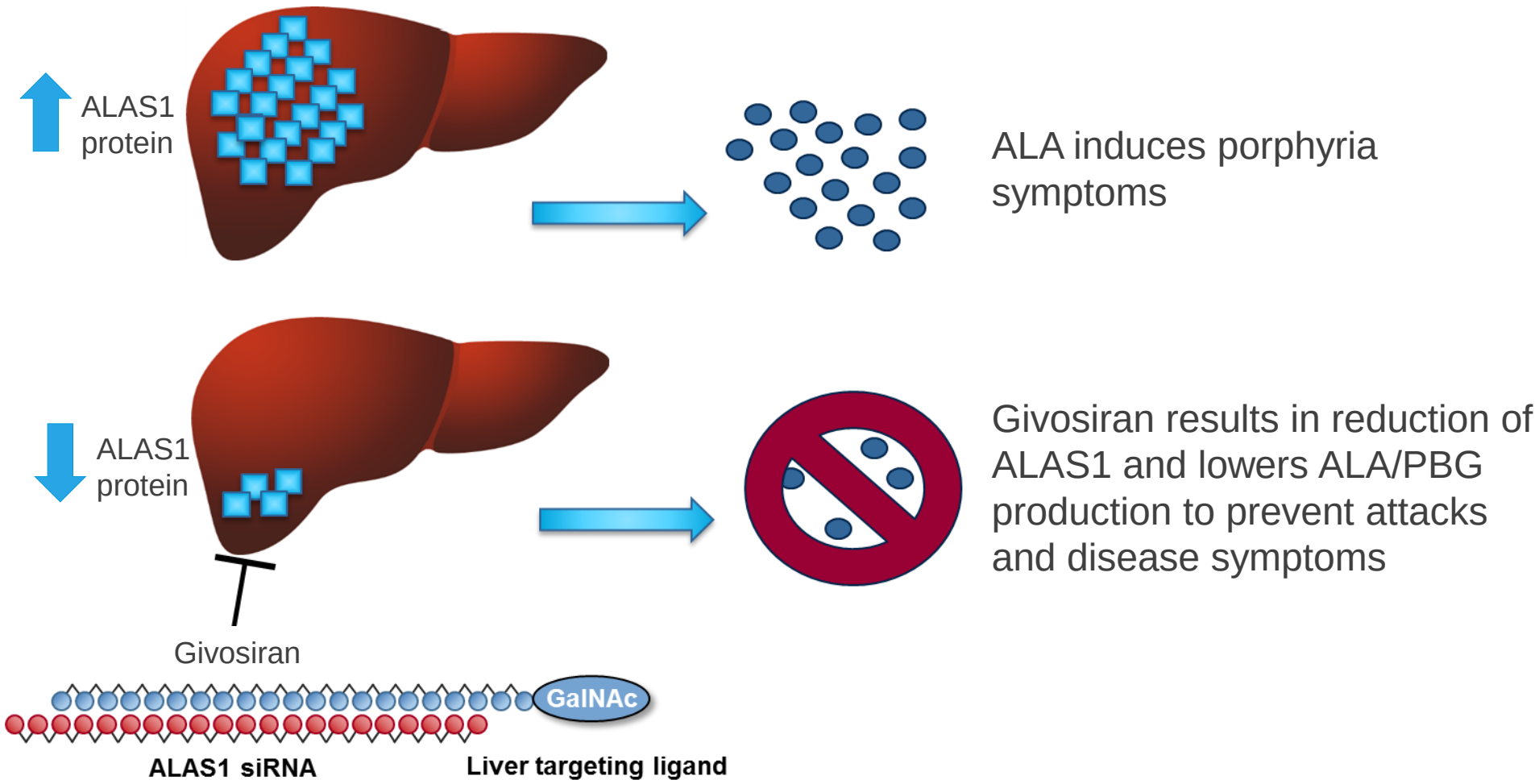
> "Before my first porphyria attack...I was active, dynamic, and cheerful…now, after the porphyria attack, the various attacks...I have unfortunately become tired, scared and lost."
>
> -AHP Patient

1. Bissell DM et al. N Engl J Med. 2017;377:862-872; 2. Ko JJ et al. ACG 2018. Poster; 3. Bylesjö I et al. Scand J Clin Lab Invest. 2009;69:612-618; 4. Bonkovsky HL et al. AASLD 2018. Poster. 5. Anderson, KE et al. Ann Intern Med. 2005; 142:439-450

Givosiran: RNAi Therapeutic for AHP

Therapeutic Hypothesis

- Reduction of Liver ALAS1 Protein to Lower ALA and PBG



AHP, Acute Hepatic Porphyria; ALA, Aminolevulinic acid; ALAS1, ALA synthase 1; PBG, Porphobilinogen.

Givosiran ENVISION Phase 3 Study

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

94 patients enrolled at 36 sites in 18 countries

Patient Population (N = 94)

- Age ≥12 years
- Diagnosis of AHP
- ≥2 attacks within prior 6 months

1:1 RANDOMIZATION

Givosiran
SC qM
2.5 mg/kg

or

Placebo
SC qM

Primary Endpoint

- Composite annualized attacks in AIP over 6 months†

Secondary Endpoints*

- ALA and PBG
- Hemin doses
- Composite annualized attacks in AHP over 6 months†
- Pain
- Fatigue
- Nausea
- PCS of SF-12

Open-Label Extension

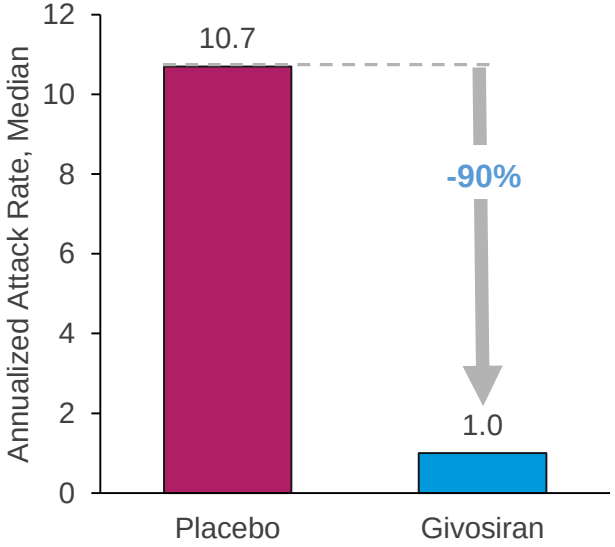
† Attacks requiring hospitalization, urgent healthcare visit, or hemin administration
* Endpoints evaluated in genetically-confirmed AIP patients, unless otherwise noted

Givosiran ENVISION Phase 3 Study

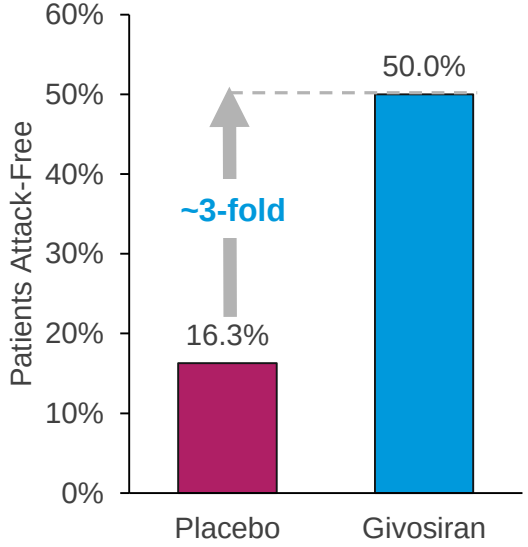
Givosiran Meets Primary Endpoint with Encouraging Profile in High Unmet Need Disease

Primary Endpoint*	Givosiran (N=46)	Placebo (N=43)	Rate Ratio	P-Value
Composite† Annualized Attack Rate, Mean	3.2	12.5	0.26	6.04×10^{-9}

Reduction in median composite attack rate



Increase in patients attack-free



Adverse Event, n of patients (%)	Placebo (N = 46)	Givosiran (N = 48)
Adverse Event (AE)	37 (80.4%)	43 (89.6%)
Serious Adverse Event (SAE)	4 (8.7%)	10 (20.8%)
Deaths	0 (0.0%)	0 (0.0%)
Discontinuations Due to AEs	0 (0.0%)	1 (2.1%)

- Two SAEs in givosiran patients reported as study drug related
  - 1 abnormal liver function test, and 1 chronic kidney disease
- Common AEs (>10% in either arm)
  - More common in givosiran than placebo: nausea, injection site reaction, chronic kidney disease, fatigue
  - More common in placebo than givosiran: headache, vomiting, urinary tract infection, pyrexia
- ALT elevations >3x ULN occurred in 7 givosiran patients compared to 1 placebo
  - Majority of ALT elevations mild to moderate in severity; occurred after the first 3 to 5 doses of givosiran
  - One givosiran-treated patient discontinued due to ALT >8x ULN, a protocol-defined stopping rule; the elevation subsequently resolved; in remaining 6 patients, all events resolved with continued dosing (n=5) or after a brief pause in dosing (n=1)
- Mild and mostly reversible increases in serum creatinine and decreases in eGFR were seen more commonly in givosiran than placebo; none led to discontinuation
- 93/94 (99%) patients enrolled into Open Label Extension (OLE) study

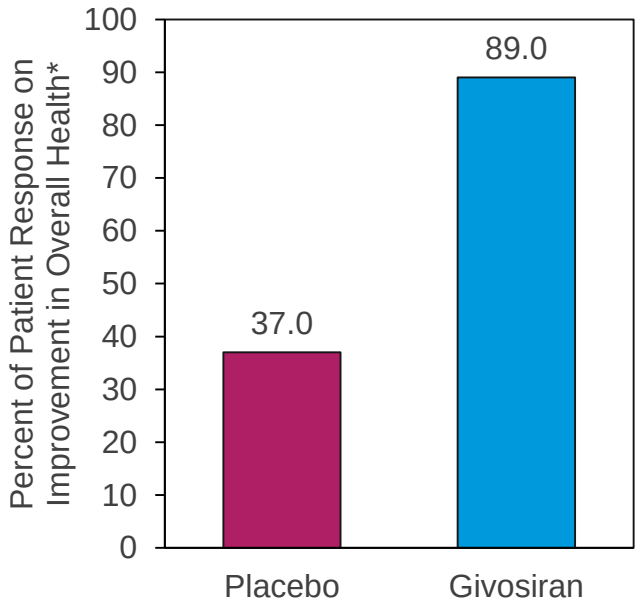
Completed primary analysis as of April 13, 2019; see Balwani, et al., EASL Meeting, April 13, 2019 for full ENVISION study results
* Efficacy endpoints evaluated in AIP patients, unless otherwise noted
† Attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home

Givosiran ENVISION Phase 3 Study

Exploratory Endpoints: AHP Patient Perspectives at Month 6

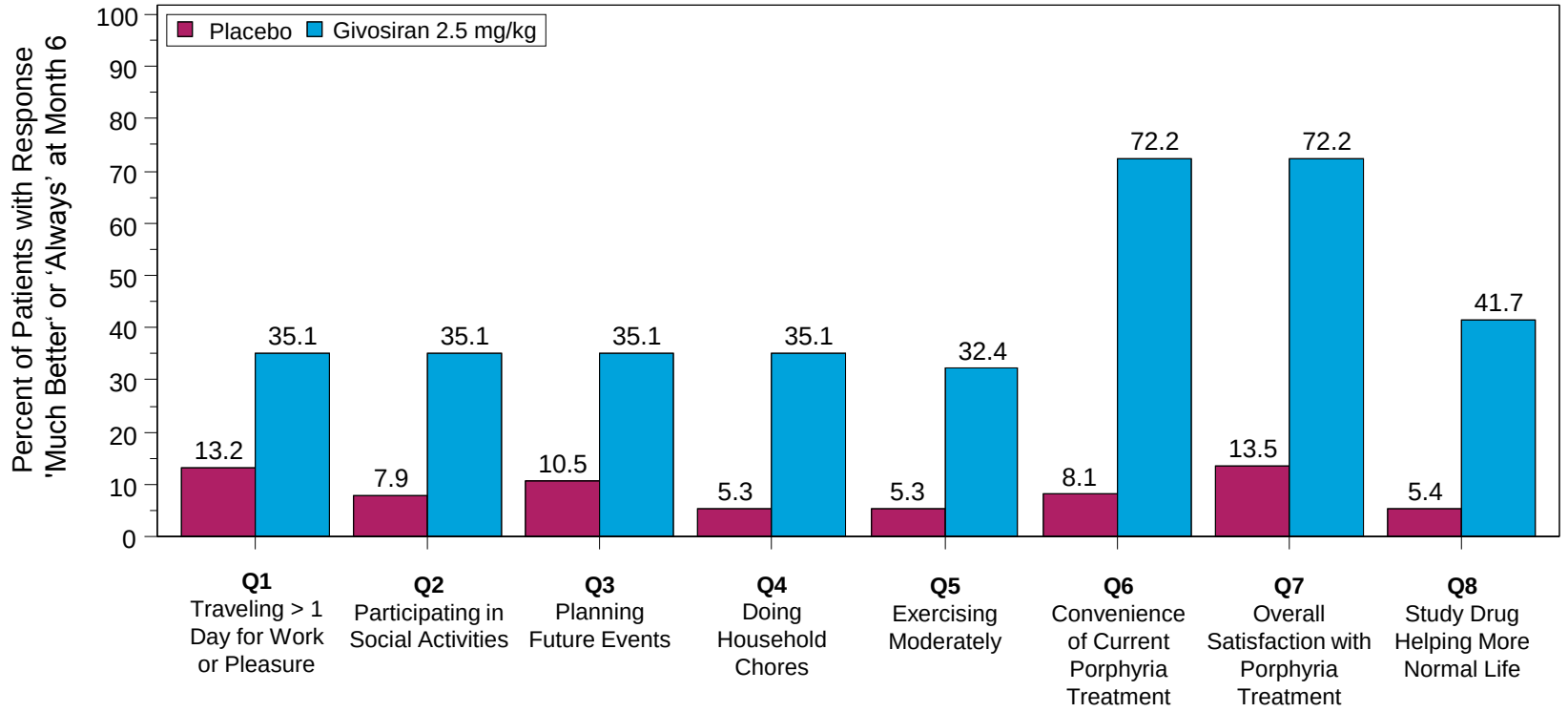
- Greater improvements in overall health status reported by givosiran patients (89%) compared to placebo (37%) as measured by Patient Global Impression of Change (PGIC) Questionnaire
- Givosiran patients report increased ability to perform daily activities and higher overall treatment satisfaction (72%) than placebo (14%) as measured by Porphyria Patient Experience Questionnaire (PPEQ)

PGIC



*Percentages reflect those patients reporting "very much improved" or "much improved"

PPEQ



Note: The figure presents the percent of patients with response 'Much Better' for Q1 to Q7 or with response 'Always' for Q8 at Month 6.

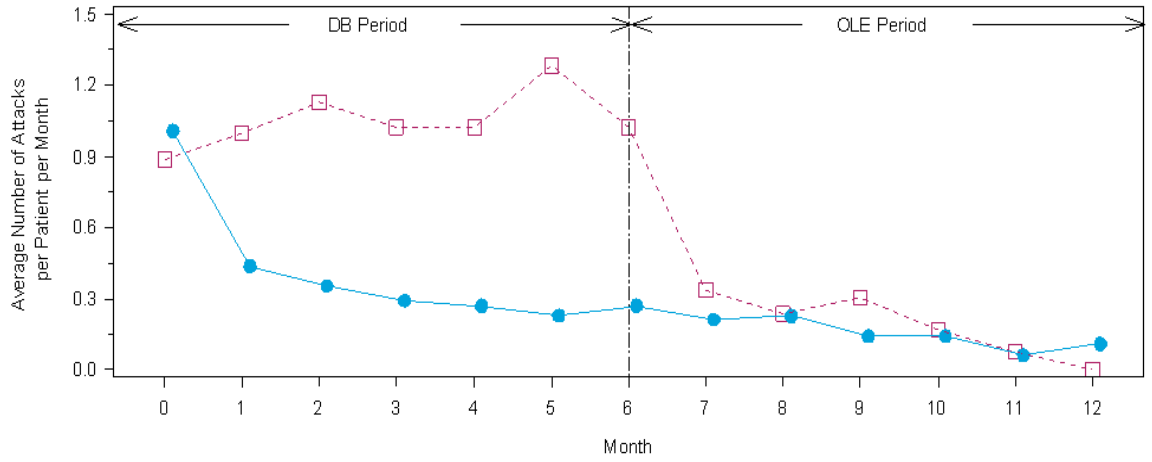
EASL, Vienna, April 13, 2019

Custom questionnaires that used global rating of change, with questions asked once at month 6, looking back at entire study period

Open-Label Extension (OLE) Period

- Maintenance of reduction of composite porphyria attack rate and urinary ALA levels in AHP patients who continued on givosiran during OLE period (blue line)
- Rapid and sustained lowering of composite porphyria attack rate and ALA levels in placebo AHP patients who crossed over to givosiran in the OLE period (red line)
- Safety profile consistent with observed profile in double-blind period

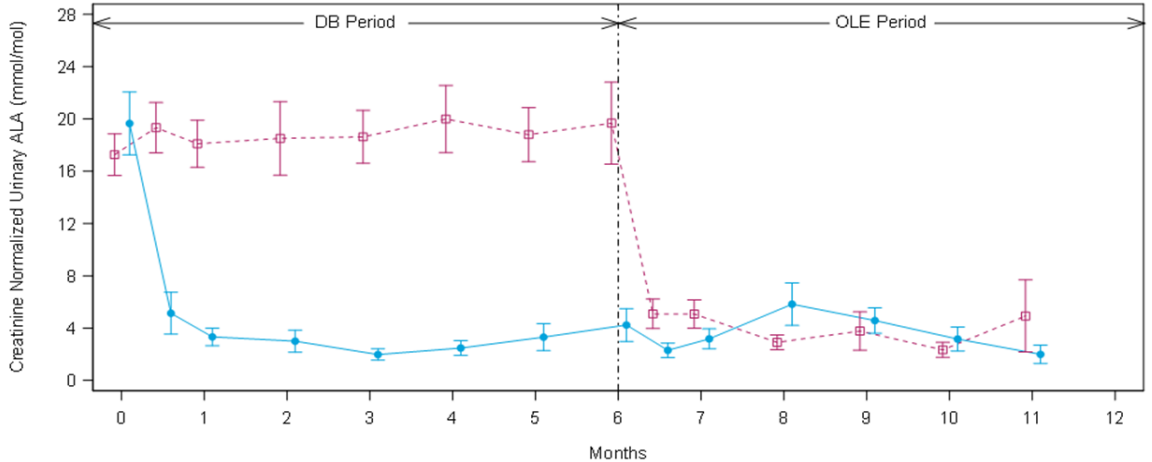
Monthly Attack Rate



No. of Patients:

Placebo	46	46	46	46	46	46	46	45	38	26	18	13	7
Givosiran	48	48	48	48	48	48	48	47	35	28	21	16	9

Urinary ALA



No. of Patients:

Placebo	46	42	44	42	45	39	44	41	40	36	26	19	13	6
Givosiran	48	47	47	48	47	45	44	46	33	33	27	20	13	8

Data cut 31 Jan 2019

NOW APPROVED

in the U.S.

GIVLAARI™

(givosiran) injection for subcutaneous use
189 mg/mL

GIVLAARI™ (givosiran) Label

Indication

GIVLAARI is indicated for the treatment of adults with acute hepatic porphyria (AHP)

Dosing & Administration

Dosing:

- 2.5 mg/kg via subcutaneous injection once monthly

Administration:

- GIVLAARI is intended for subcutaneous use only by a healthcare professional

Safety*

Contraindications

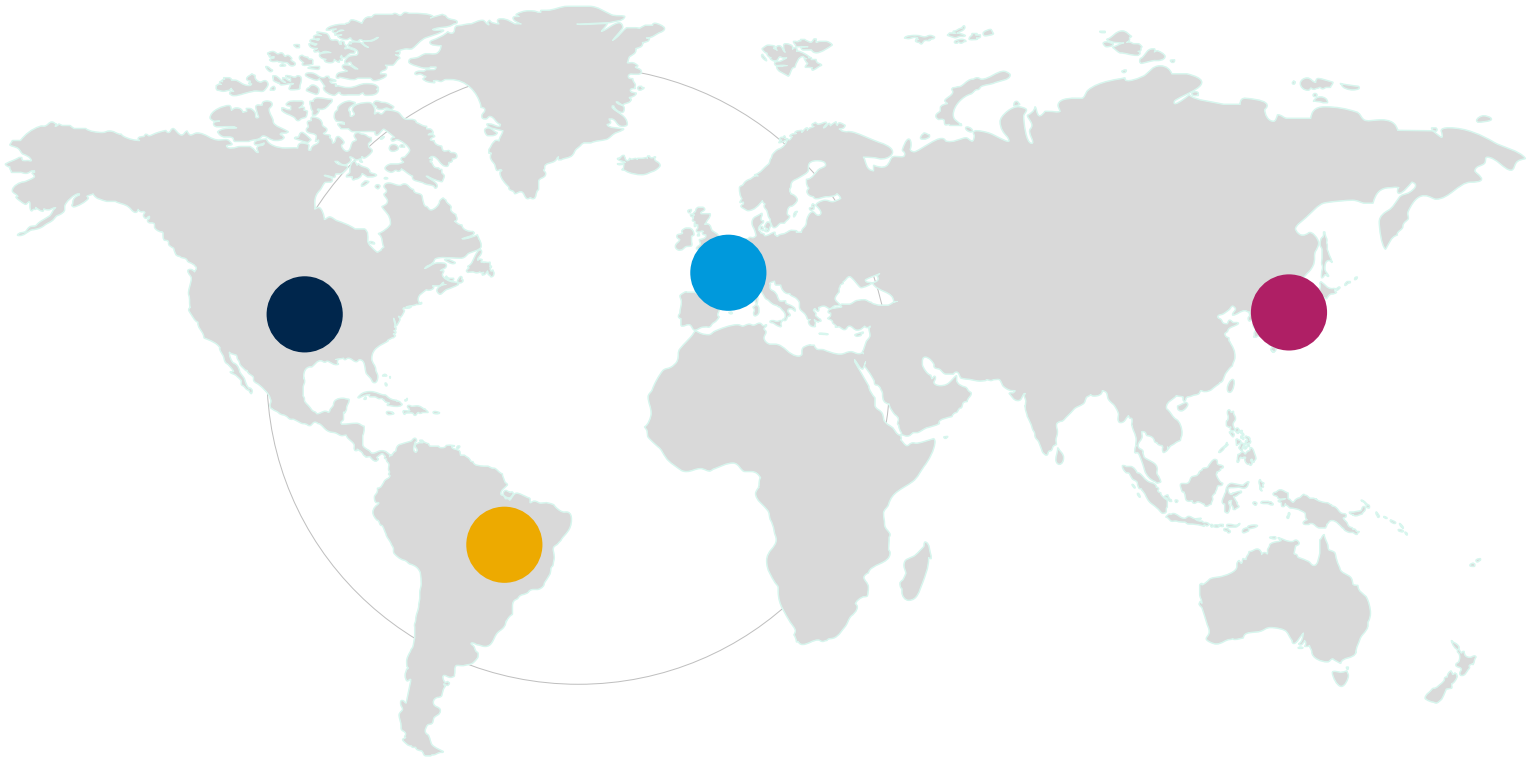
- GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran

Warnings and Precautions

- Anaphylactic Reaction: Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms. If anaphylaxis occurs, discontinue GIVLAARI and administer appropriate medical treatment.
- Hepatic Toxicity: Measure liver function at baseline and periodically during treatment with GIVLAARI. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations.
- Renal Toxicity: Monitor renal function during treatment with GIVLAARI as clinically indicated.
- Injection Site Reactions: May occur, including recall reactions. Monitor for reactions and manage clinically as needed.

* For additional Important Safety Information on GIVLAARI, see full Prescribing Information

Status and Path Forward



Approved in U.S.

Under review by EMA in EU
- Potential launch early 2020

Filing submitted in Brazil
- Potential approval late 2020

Continue global regulatory filings
- Planned filing in Japan in late 2020
- Potential launches in Japan and ROW in 2021 and beyond

Acute Hepatic Porphyria

GIVLAARI™ (givosiran)

Program Overview

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

Commercial Plans

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

NOW APPROVED

in the U.S.

GIVLAARI™

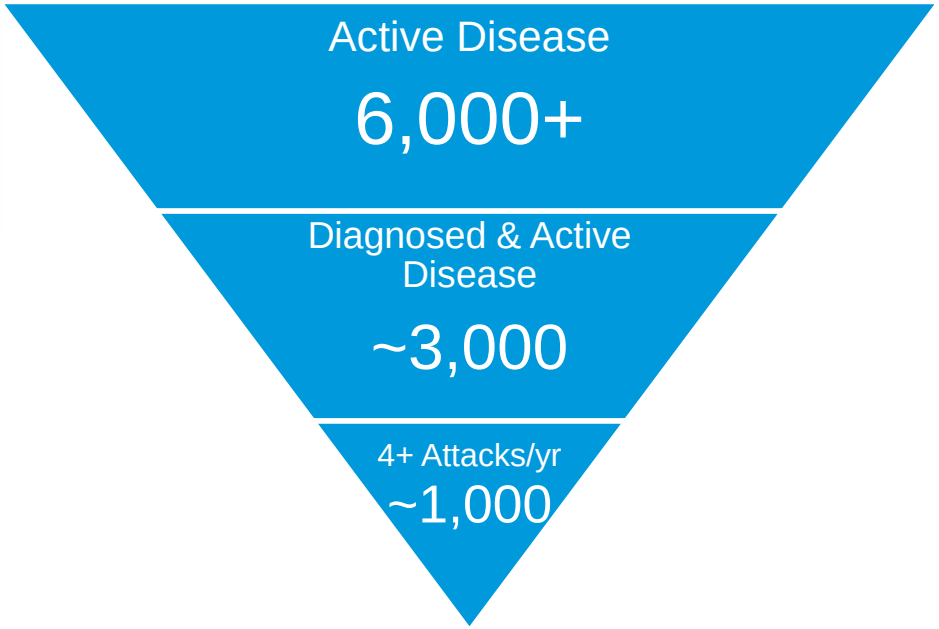
(givosiran) injection for subcutaneous use
189 mg/mL

GIVLAARI™ (givosiran) Market Opportunity

Estimated Prevalence and Addressable Population*

MUTATION PREVALENCE[1,2]	DISEASE PREVALENCE[3]	DIAGNOSED PREVALENCE[4,5]	DIAGNOSED & ACTIVE DISEASE†[,5]
~1 per 1,700	~20-50 per Million (Global)	~10 per Million (U.S./EU)	~5 per Million (U.S./EU)

Patients in U.S./EU

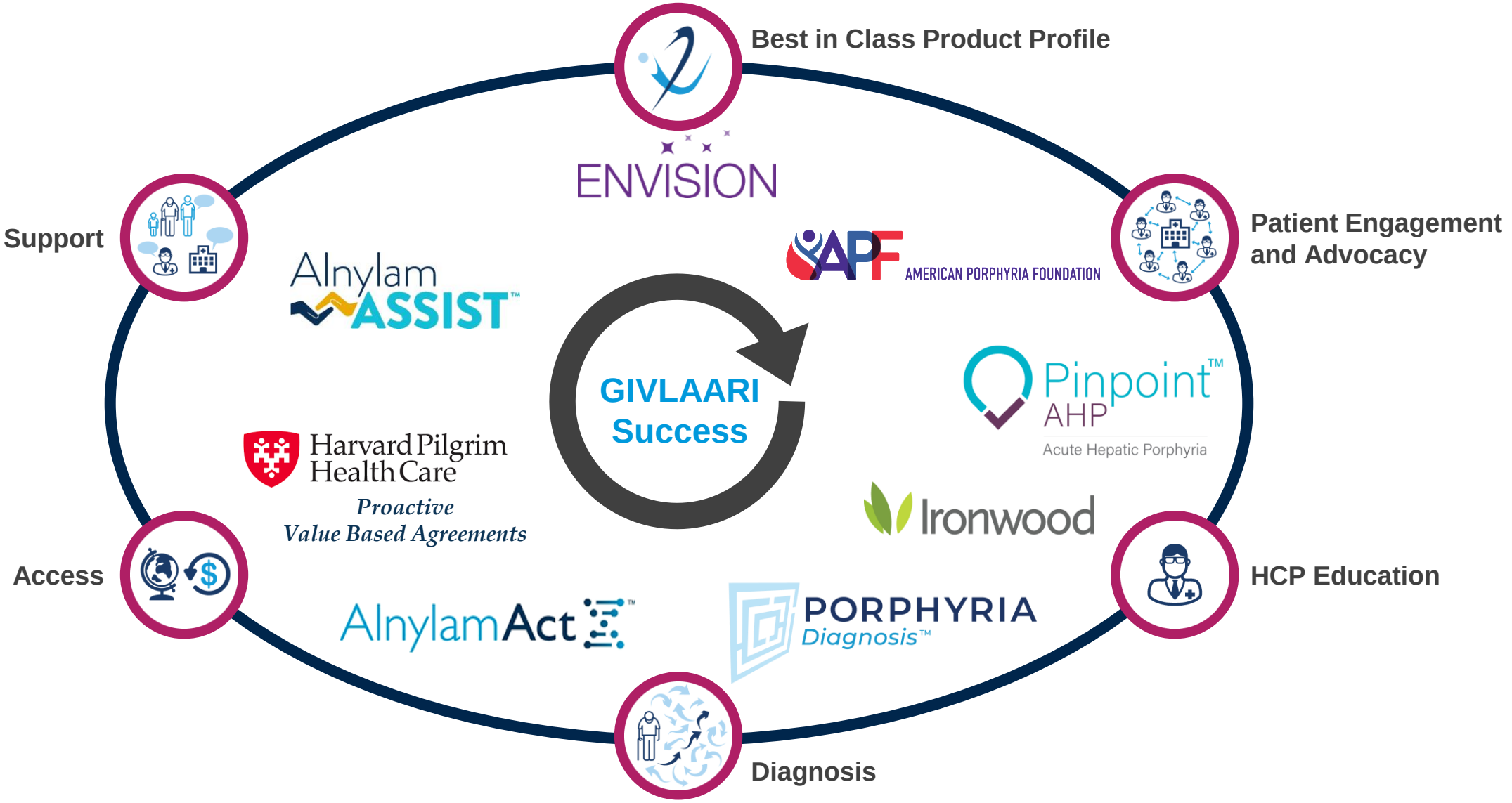


Opportunity for growth over time with increased diagnosis and global commercial expansion

1 Nordmann et al. J Intern Med 1997;242:213–7
2 Chen et al. Hum Mutat 2016;37:1215–222;
3 Anderson KE, Metabolic & Molecular Bases of Inherited Disease, 2001;
4 Elder et al. J Inherit Metab Dis 2013;36:849–57; 5. Data on file, IBM MarketScan Commercial Claims and Medicare Supplemental Database
† Patients with 1 or more attacks in past 12 months
* Per U.S. Prescribing Information, GIVLAARI is indicated for the treatment of adults with AHP

Educating on AHP and Launching GIVLAARI Globally

Leveraging ONPATTRO Capabilities



AHP Disease Awareness Initiatives Ongoing

- Includes Pinpoint AHP.com, Dr. Discussion Guide, and MOD Video
- Disease Awareness Patient Ambassador stories
- AHP Brochure (print and digital)
- SEO and Banner Ads ➡ CRM registration
- AHP Disease Awareness Webinars
- **>10,000** people have registered for updates

DISEASE AWARENESS THRU IRONWOOD

MOD: mechanism of disease; **SEO:** search engine optimization; **CRM**: customer relationship management

Market Research: HCPs Motivated to Prescribe GIVLAARI for Patients

Respondents said that GIVLAARI **meets a highly felt unmet need for a prophylaxis** treatment for AHP

Patients who suffer attacks risk having a lower quality of life – a prophylaxis agent would provide needed relief

- Attacks are painful and hospitalizations are disruptive
- Patients tend to be young women of childbearing ages who lead busy work and family lives, therefore particularly impacted
- **Each acute attack has potential to damage internal organs, which over time can add up to serious health complications**

"It is a preventative treatment for those patients who are having symptoms quite frequently. That is a good thing as we are avoiding the patient having to be hospitalized every time they have an attack."
(Gastroenterologist)

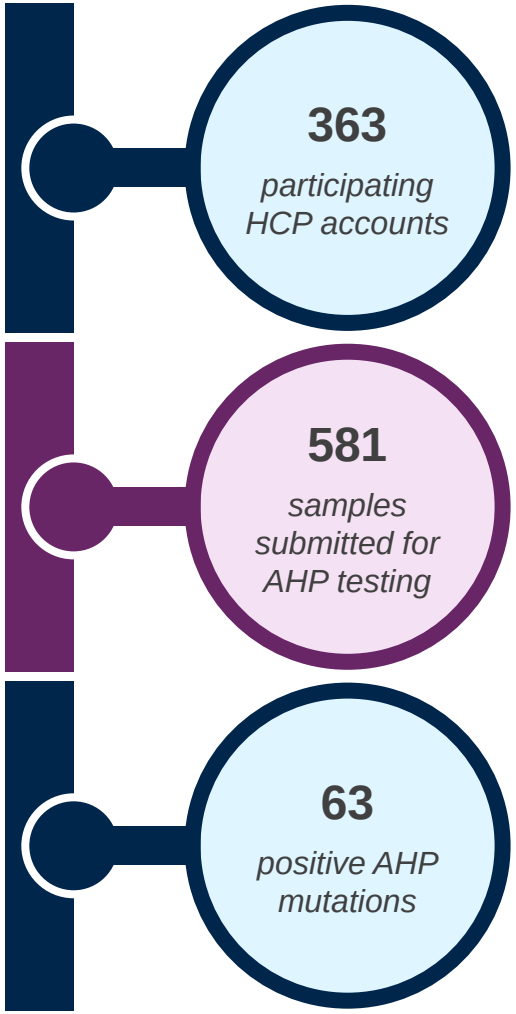
Respondents saw GIVLAARI as a one of a kind, **novel therapy**

- **No treatment currently approved for prophylactic benefit**
- Some HCPs specifically refer to it as a **targeted** treatment – working to stop underlying problem at molecular level rather than just treating symptoms

"We are changing our approach to therapy; from a replacement therapy to a targeted therapy."
(HemOnc)

Alnylam Act – Acute Hepatic Porphyria

Third-Party Genetic Testing and Counseling Program Sponsored by Alnylam



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

Tests and services are performed by independent third parties

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

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

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

Data as of October 2019

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

Pricing, Cost & Access Considerations

TREATMENT EFFECT

Shown to reduce rate of porphyria attacks by >70% compared to placebo, with potential to substantially benefit QOL

UNMET NEED

First of its kind FDA-approved treatment for adult patients with all types of AHP

INNOVATIVE PRICING

Proactively seeking VBAs with PBA option to link value delivered with real world drug performance and patient prevalence

ULTRA RARE DISEASE

~3,000 patients currently diagnosed in U.S./EU with active disease

COST OF CARE OFFSETS

Demonstrated attack reduction with potential to reduce hospitalization rate, need for acute treatment ($400,000 - $650,000 cost/year for many patients)

PATIENT ACCESS

Maximize patient access relative to anticipated insurance make-up, consistent with Alnylam Patient Access Philosophy

Average Annual List Price
$575,000
– $39,000 per vial

Average Effective Net Price
$442,000

- Based on average weight-based dose of **1.2 vials** per patient in ENVISION
- Before mandatory rebates to government institutions
- Price may vary per individual insurance coverage and dosing

GIVLAARI™ (givosiran) Market Opportunity

Ultra-Rare Orphan Disease with Significant Disease Burden and Limited Treatment Options

PREVALENCE	DIAGNOSIS	DISEASE BURDEN	COST BURDEN
~3,000	**~20-50%**	**65%**	**$400–650K**
patients in U.S./EU, diagnosed with active disease[1,2]	currently diagnosed; delays up to 15 years	recurrent attack patients with chronic symptoms[3]	average annual expenditure, recurrent attack patients[4]

GIVLAARI | ACUTE HEPATIC PORPHYRIA

>$500M potential market opportunity

1 Elder et al. J Inherit Metab Dis 2013;36:849–57
2 Data on file, IBM MarketScan Commercial Claims and Medicare Supplemental Database
3 Gouya, et al. EASL 2018
4 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 U.S.

Q&A Session #1

10:30 – 10:50 AM

Moderator:

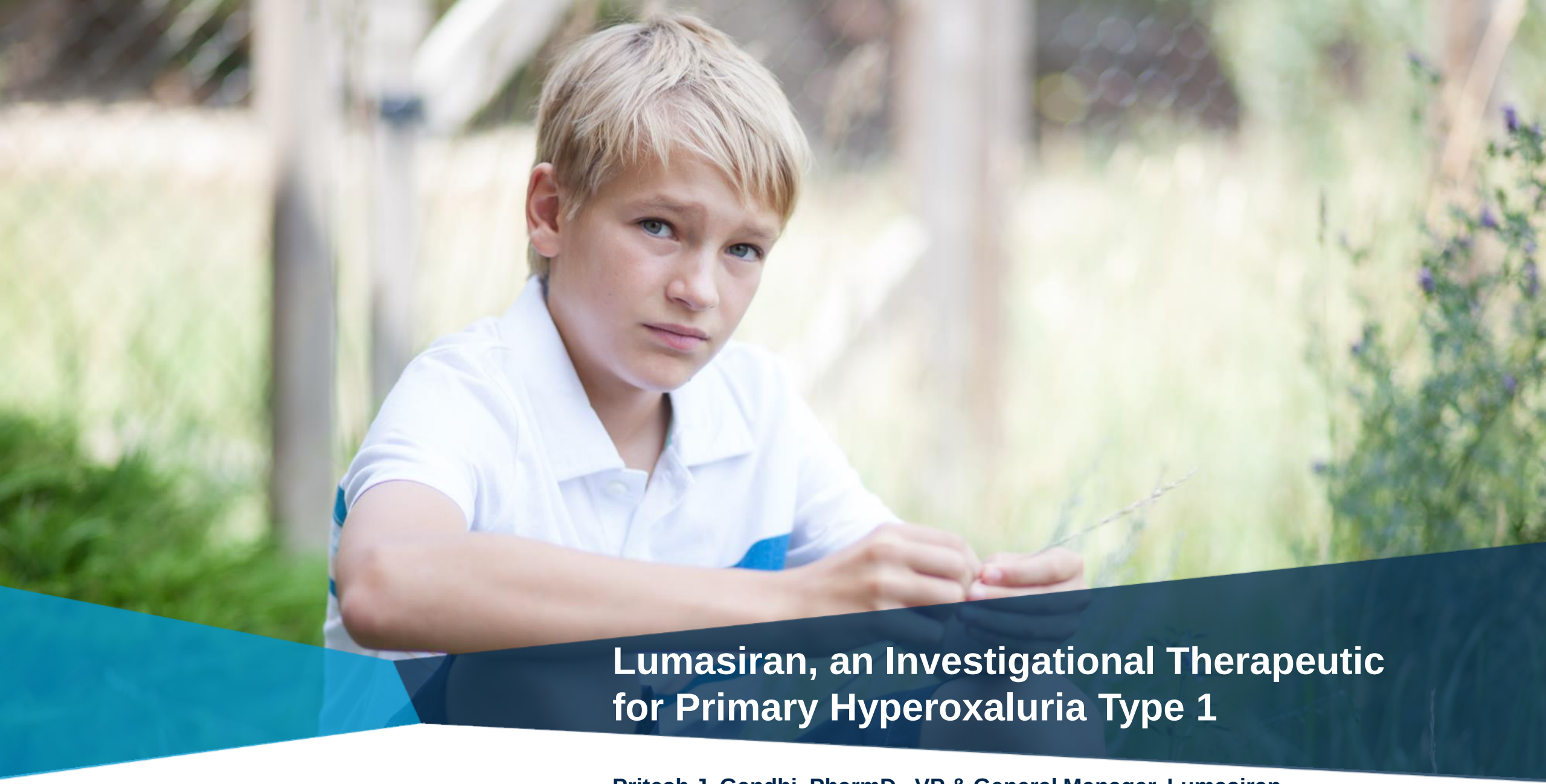
- Barry Greene, President

Panelists:

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

Break

Presentations to Resume at 11:05 am



Lumasiran, an Investigational Therapeutic for Primary Hyperoxaluria Type 1

Pritesh J. 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

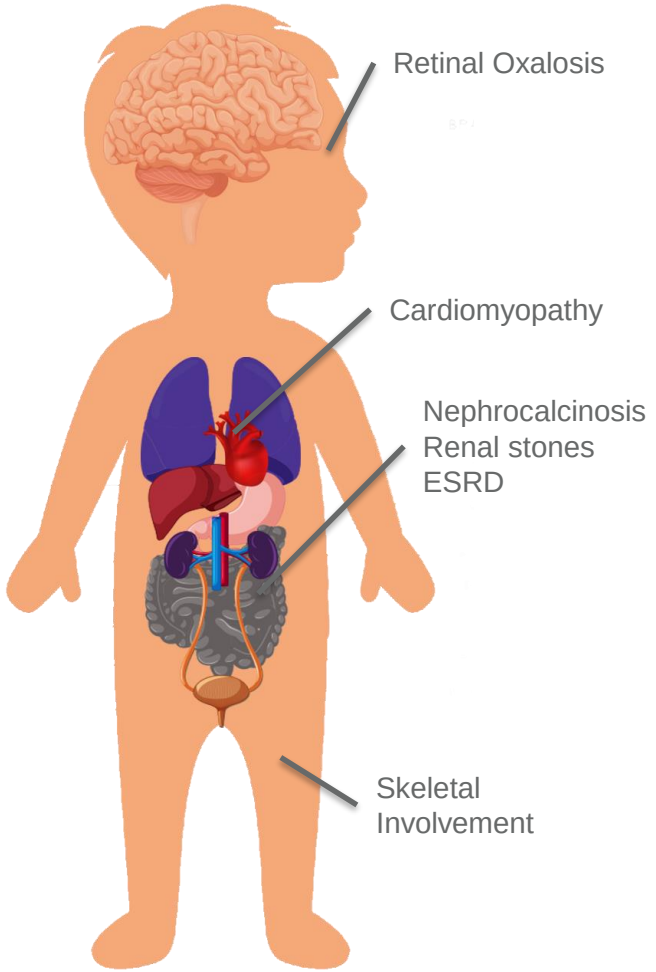
pediatric

very limited treatment options

Patient Population

~3,000 – 5,000

U.S./EU



Distribution of Clinical Manifestations Based on Age and Renal Function

26%

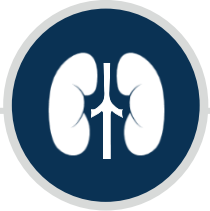
Infantile oxalosis and rapid progression to **renal failure** before one-year of age

30%

Recurrent **urolithiasis** associated with **rapid decline in renal function** in childhood and adolescence

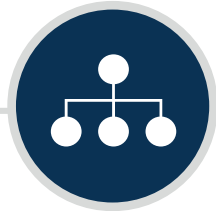
21%

Occasional **stone events** in adulthood with **mild-to-moderate renal dysfunction**



10%

Diagnosis after **recurrence of disease post-kidney transplant**



13%

Individuals with a **positive family history** who may be mildly symptomatic

Harambat, J., et al. Kidney Int, 2010. 77(5): p. 443-9.

Patient Needs Constrained by Limitations of Current Management Strategies

No Approved Therapies for PH1

Current standard of care seeks to reduce UOx; however**, >80% of PH1 cases lead to loss of renal function**

Intensive dialysis in PH1:

- **Can impose an extreme burden**
- **May not consistently lower plasma oxalate in patients with advanced disease**

Current standard of care can be partially effective and requires intensive chronic care

- High fluid intake
- Dietary restrictions

Combined liver-kidney transplant corrects metabolic derangement, but carries **significant burden and risks**, including risk of death

1. Milliner DS et al. In: GeneReviews. [updated November 30, 2017]. https://www.ncbi.nlm.nih.gov/books/NBK1283. Accessed June 18, 2018; 2. Hoppe B. Kidney Int. 2010;77(5):383-385; 3. Mandrile G et al. Kidney Int. 2014;86(6):1197-1204; 4. Hamm LL. Kidney Int. 1990;38:728-735; 5. Leumann E et al. Nephrol Dial Transplant. 1995;10[suppl 8]:14-16; 6. Cochat P et al. Nephrol Dial Transplant. 2012;27(5):1729-1736; 7. Edvardsson VO, et al. Pediatr Nephrol. 2013;28(10):1923-1942; 8. Cochat P, Groothoff JW. Pediatr Nephrol. 2013;28(12):2273-2281.

Primary Hyperoxaluria Type 1 and Lumasiran Therapeutic Hypothesis

Pathophysiology:

- Due to defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)

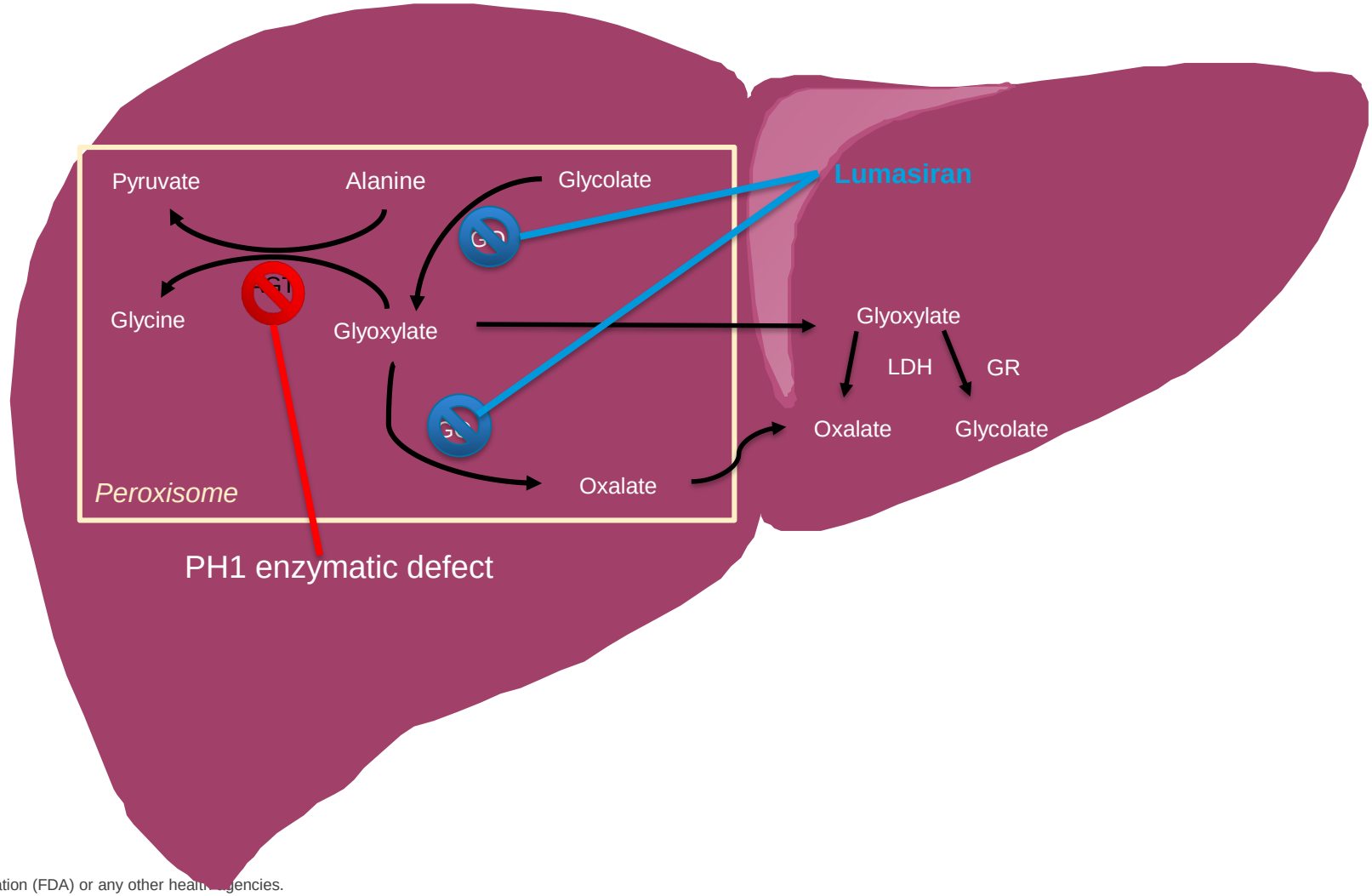
Lumasiran (ALN-GO1):

- Investigational SC-administered small interfering RNA (siRNA)
  - Harnesses natural RNA interference (RNAi) mechanism

Therapeutic Hypothesis:

- Lumasiran targets the mRNA for HAO1 which encodes glycolate oxidase (GO) in the liver; the decreased production of GO reduces hepatic oxalate production

Lumasiran Therapeutic Hypothesis:



HAO1, hydroxyacid oxidase 1

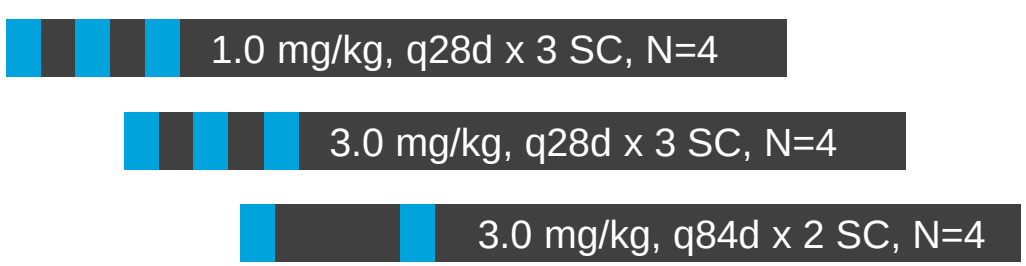
Liebow A, et al. J Am Soc Nephrol. 2017.

The safety and efficacy of lumasiran have not been evaluated by the U.S. Food and Drug Administration (FDA) or any other health agencies.

Lumasiran Phase 1/2 Study†

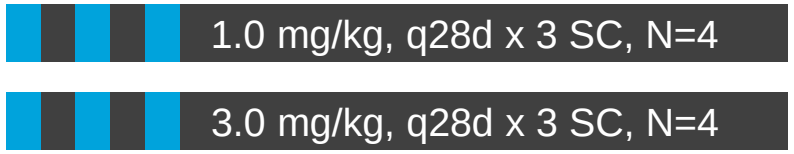
Study Design & Demographics: Part B (Patients with PH1)

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



Patients randomized to placebo received subsequent dosing of lumasiran

Expansion Cohorts | Open-label



Inclusion Criteria:

- Patients with PH1
- Ages 6-64 years
- eGFR > 45 ml/min/1.73m^2
- Urinary oxalate excretion > 0.70 mmol/24h/1.73m^2

Key Endpoints:

- Safety and tolerability
- Urinary oxalate excretion
- Urinary oxalate to creatinine ratio

After median follow up of 9.8 months (range: 5.6 – 15.2), all patients enrolled in an open-label extension (OLE) study# for long-term dosing

†NCT02706886; #NCT03350451
eGFR, estimated glomerular filtration rate

Lumasiran Phase 1/2 Study

Patient Demographics: Part B (Patients with PH1)

Baseline Characteristics	Result (N=20)
Mean age, years (range)	14.9 (6–43)
Age <18 years	80%
Gender, females	65%
Mean weight, kg (range)	50.0 (21.3–112.5)
Mean eGFR, mL/min/1.73m^2 (range)	77.3 (42.5 –130.7)
Mean Urine Oxalate Content, mmol/24hr/1.73m^2 (range)	1.69 (0.83–2.97)
Mean 24-hour Urine Oxalate:Creatinine Ratio (range)	0.17 (0.07–0.30)

Oxalosis & Hyperoxaluria (OHF) International Workshop, Boston, MA, 22 June 2019

eGFR, estimated glomerular filtration rate

Lumasiran Phase 1/2 Study Results

Safety: Part B (Patients with PH1)

Multiple doses of lumasiran well tolerated in patients with PH1

- No discontinuations from study treatment
- SAEs reported in 1 (33%) patient during placebo dosing and 4 (20%) patients after lumasiran dosing; none considered related to study drug by investigator
- AEs reported in 2 (66.7%) patients during placebo dosing and 20 (100%) patients after lumasiran dosing
  - Majority of AEs were mild or moderate in severity and considered unrelated to study drug by investigator
  - AEs reported in >3 patients receiving lumasiran: pyrexia (N=6); vomiting, cough, abdominal pain, headache (N=5 each); and rhinitis and nephrolithiasis (N=4 each)
  - Self-limiting injection site reactions (ISRs) reported in 3 (15%) patients receiving lumasiran; all mild or moderate and none affected dosing
- No clinically significant laboratory changes

Oxalosis & Hyperoxaluria (OHF) International Workshop, Boston, MA, 22 June 2019

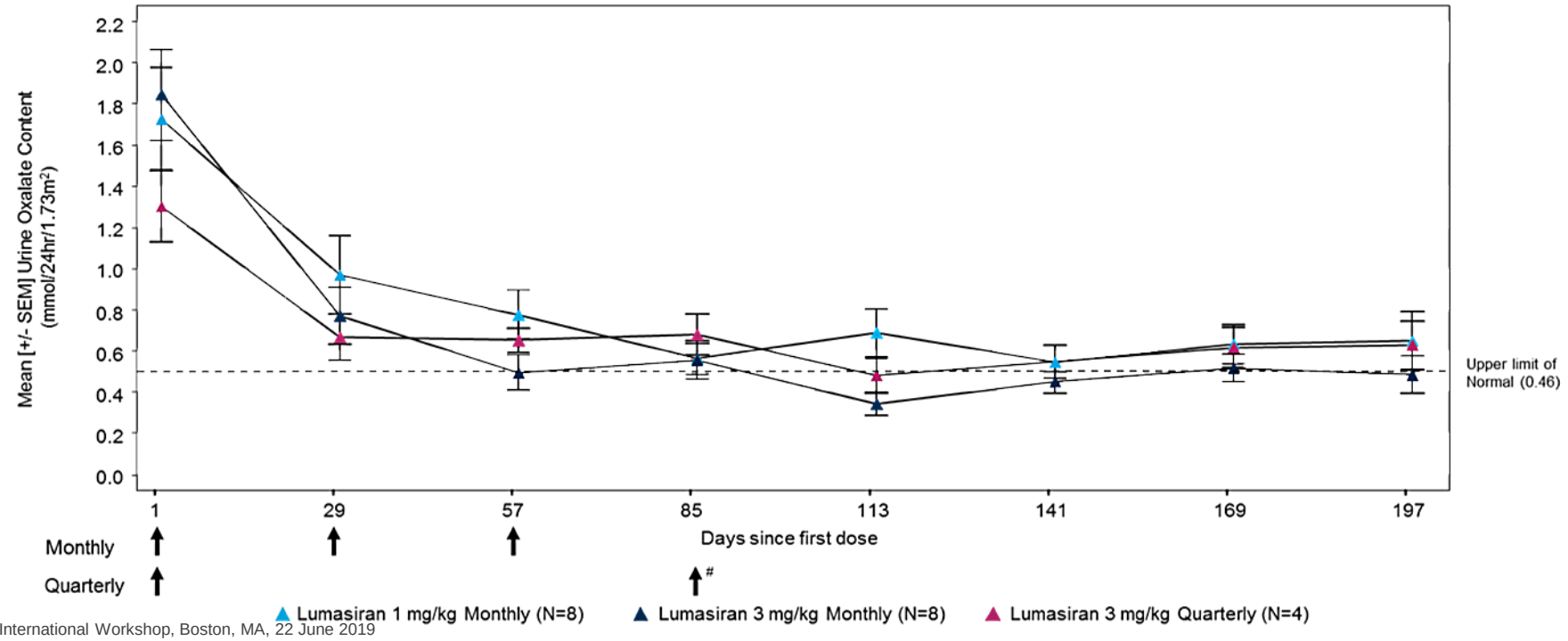
SAE, serious adverse event

Lumasiran Phase 1/2 Study Results

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

Mean maximal reduction in urinary oxalate of 75% (range: 43-92%) relative to baseline after lumasiran dosing in all cohorts† (N=20)

- The mean reduction relative to baseline 28 days post last dose of lumasiran was 66%
- 100% of patients achieved a urinary oxalate level ≤1.5x ULN and 70% of patients achieved a urinary oxalate level within the normal range‡
  - Among patients receiving 3.0 mg/kg monthly or quarterly doses of lumasiran, 11/12 (92%) achieved urinary oxalate levels within the normal range



Oxalosis & Hyperoxaluria (OHF) International Workshop, Boston, MA, 22 June 2019

Only data points with at least 3 contributing patients are represented.

†Patients who had a valid 24-hour urinary oxalate assessment; placebo data not shown due to limited valid collections

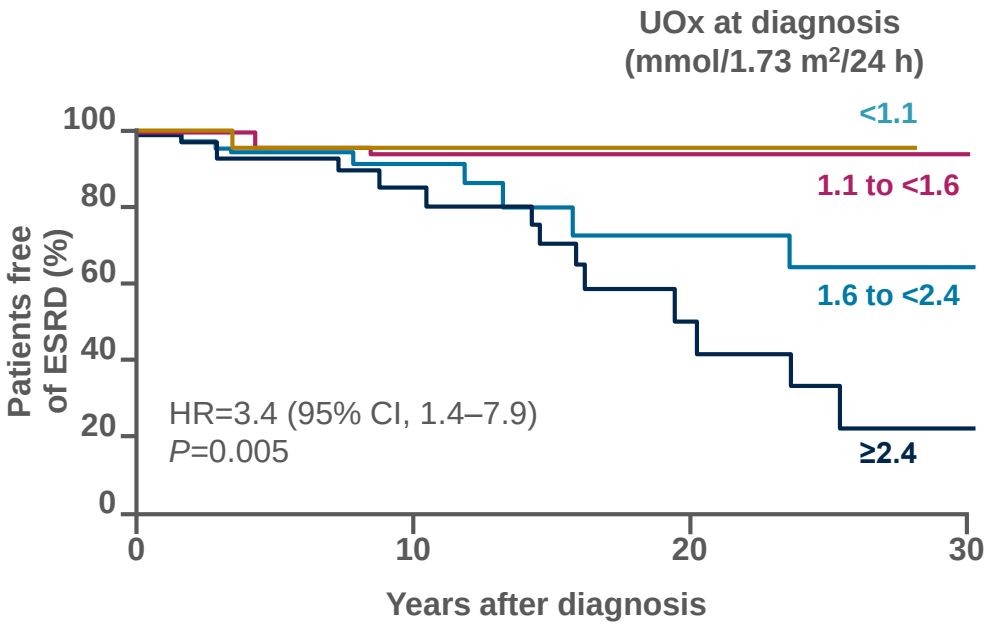
‡1.5x ULN is defined as 0.69 mmol/24hr/1.73m2; normal range is defined as ≤0.46 mmol/24hr/1.72m2

#Patients randomized to placebo received subsequent dosing of lumasiran and are included in the lumasiran dosing cohort in which they were randomized with day 1 relative to first dose of lumasiran; patient randomized to placebo in 3 mg/kg quarterly dosing only received a single dose of lumasiran on Day 1

ULN, upper limit of normal

Potential Significance of Decreasing Urinary Oxalate

- 192 patients with PH from a retrospective cohort study
- Renal survival was examined by quartile of urine oxalate (UOx) excretion (mmol/24hr/1.73m^2)
- Renal survival estimates were lower in patients with higher levels of UOx excretion



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

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

Lumasiran Phase 1/2 and Phase 2 OLE

Patients completing Phase 1/2† study eligible to enroll into Phase 2^ open-label extension (OLE) study

- All patients enrolled in Phase 1/2 completed and enrolled in OLE (N=20)
  - Data presented here represent 20 patients dosed in Phase 2 OLE, as of 12 Sep 2019
- All patients have been on study for a median of 10.4 months (range: 7 – 17; N=20)

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

- 1.0 mg/kg, monthly x 3 SC, N=8
- 3.0 mg/kg, monthly x 3 SC, N=8
- 3.0 mg/kg, quarterly x 2 SC, N=4

Phase 2 OLE (N=20)

- 1.0 mg/kg, monthly SC, N=3*
- 3.0 mg/kg, monthly SC, N=7
- 3.0 mg/kg, quarterly SC, N=10

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

ASN 2019 Annual Meeting, Washington D.C., 09 November 2019

*At time of data cut, all patients have transitioned to 3.0 mg/kg quarterly dosing

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

Lumasiran Phase 2 OLE Study Results

Safety

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

- No discontinuations from study treatment

- A single patient (1/20; 5.0%) reported 2 SAEs (traumatic brain injury and bone contusion sustained during car accident); none assessed as related to study drug

- AEs reported in 19/20 (95%) of patients; majority were reported in single patients
  - Majority of AEs were mild in severity and assessed as unrelated to study drug
  - AEs reported in more than 1 patient were: injection site reaction (n=4); headache, oropharyngeal pain (n=3); gastroenteritis, viral gastroenteritis, pyrexia, vomiting (n=2)
  - 4/20 (20%) patients reported injection site reactions; all were mild and assessed as related to study drug

- No clinically significant laboratory changes

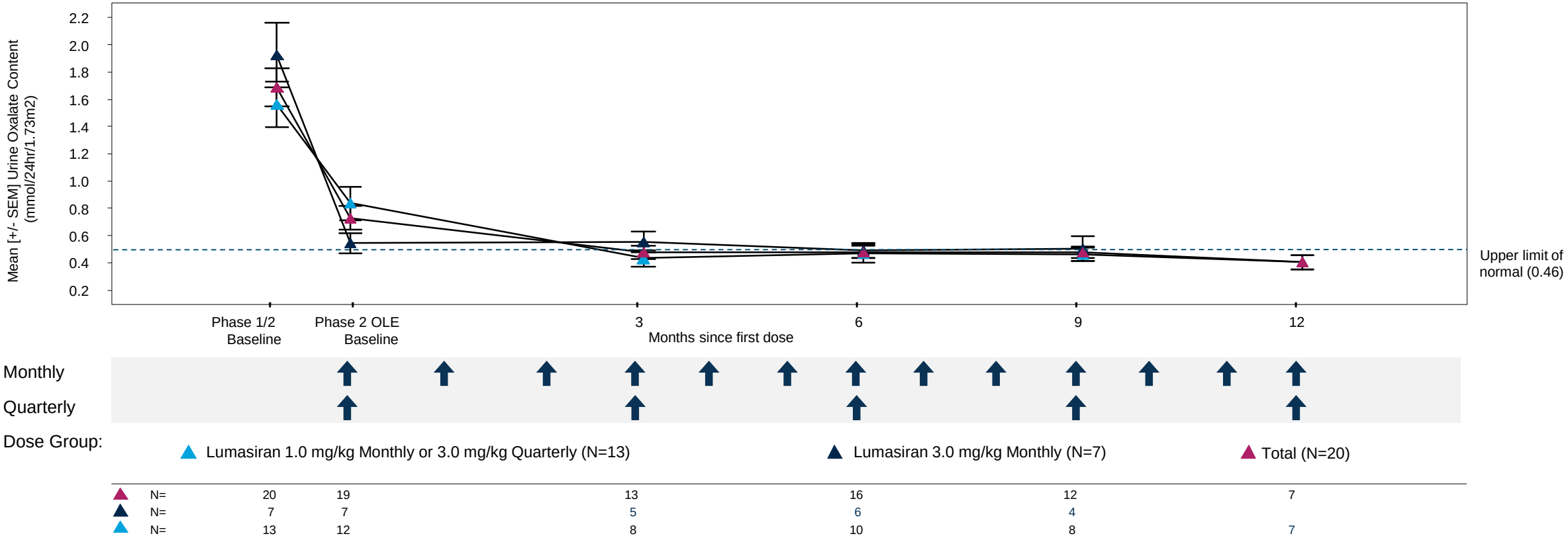
T. McGregor, presented at the ASN 2019 Annual Meeting, Washington D.C., 09 November 2019
Data cut-off: 12 Sep 2019; SAE, serious adverse event

Lumasiran Phase 2 OLE Study Results

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

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

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



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

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

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

Lumasiran Registrational Program

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

ILLUMINATE

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

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

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

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

EAP - NCT04125472

Lumasiran ILLUMINATE•A Phase 3 Study

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

ENROLLMENT COMPLETED

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 >30 mL/min/1.73m^2

2:1 RANDOMIZATION

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

or

Placebo
3xqM loading dose, then q3M SC

Primary Endpoint

- Percent change from baseline through Month 6* in 24-hour urinary oxalate corrected for body surface area

Open-Label Extension

ILLUMINATE•A

Lumasiran has received FDA Breakthrough and EMA PRIME Designations

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

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

NCT03681184; EudraCT Number: 2018-001981-40

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

*average of 24h UOx of months 3-6

Lumasiran ILLUMINATE•B Phase 3 Study

Open-Label Study in Pediatric Primary Hyperoxaluria Type 1 Patients

NOW ENROLLING

Patient Population (N=20)

- Infants and children <6 years
- Elevated urinary oxalate:creatinine ratio
- Confirmed alanine glyoxylate aminotransferase (*AGXT*) mutation
- eGFR >45 mL/min/1.73 m^2 if ≥12 months old; non-elevated serum creatinine if <12 months old

Open-Label

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

Primary Endpoint

- Percent change from baseline through Month 6* in 24-hour urinary oxalate corrected for body surface area

Open-Label Extension ‡

ILLUMINATE•B

Lumasiran has received FDA Breakthrough and EMA PRIME Designations

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

NCT03905694; EudraCT Number: 2018-004014-17

†Patients <10 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 3.0 mg/kg, Patients ≥10 kg to <20 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 6.0 mg/kg, Patients ≥20 kg: Three monthly loading doses at 3.0 mg/kg then maintenance dose of 3.0 mg/kg

‡Continued weight-based dosing using weight obtained 7 days prior to dosing; *average of 24h UOx of months 3-6

Lumasiran ILLUMINATE•C Phase 3 Study

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

NOW ENROLLING

Patient Population (N=16)

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

Open-Label

Lumasiran
(Cohort A – No hemodialysis)

Three monthly loading doses then maintenance dosing dependent on weight†

Lumasiran
(Cohort B – Hemodialysis)

Three monthly loading doses then maintenance dosing dependent on weight†

Primary Endpoint

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

Open-Label Extension ‡

ILLUMINATE•C

Lumasiran has received FDA Breakthrough and EMA PRIME Designations

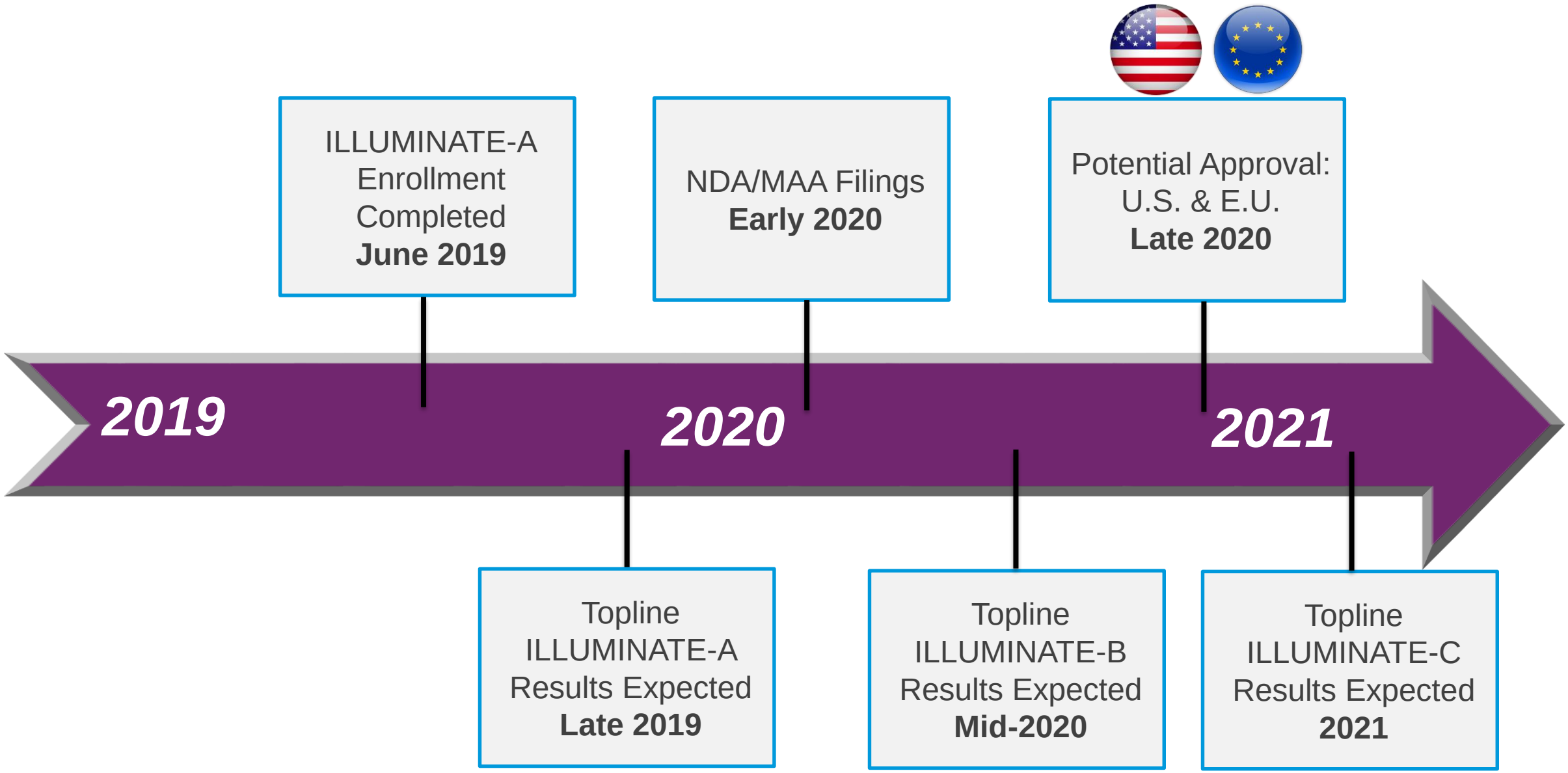
Topline ILLUMINATE-C results expected **2021**

NCT04152200; EudraCT Number: 2019-001346-17

†Patients <10 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 3.0 mg/kg, Patients ≥10 kg to <20 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 6.0 mg/kg, Patients ≥20 kg: Three monthly loading doses at 3.0 mg/kg then maintenance dose of 3.0 mg/kg

‡Continued weight-based dosing using weight obtained 7 days prior to dosing

Potential Timeline for Topline Phase 3 Data and Potential Initial Approval



Aiming to Address Unmet Need by Improving Diagnosis & Care

Increasing PH1 Awareness

Education Initiatives Developed for Physicians

Launch of Children's Animation Video Series for PH1

Learn more at ph1ofakind.com

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

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

Kim Hollander – Executive Director, OHF

Lumasiran Market Opportunity

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

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

LUMASIRAN | PRIMARY HYPEROXALURIA TYPE 1

>$500M potential market opportunity

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

Next Wave of RNAi Opportunities

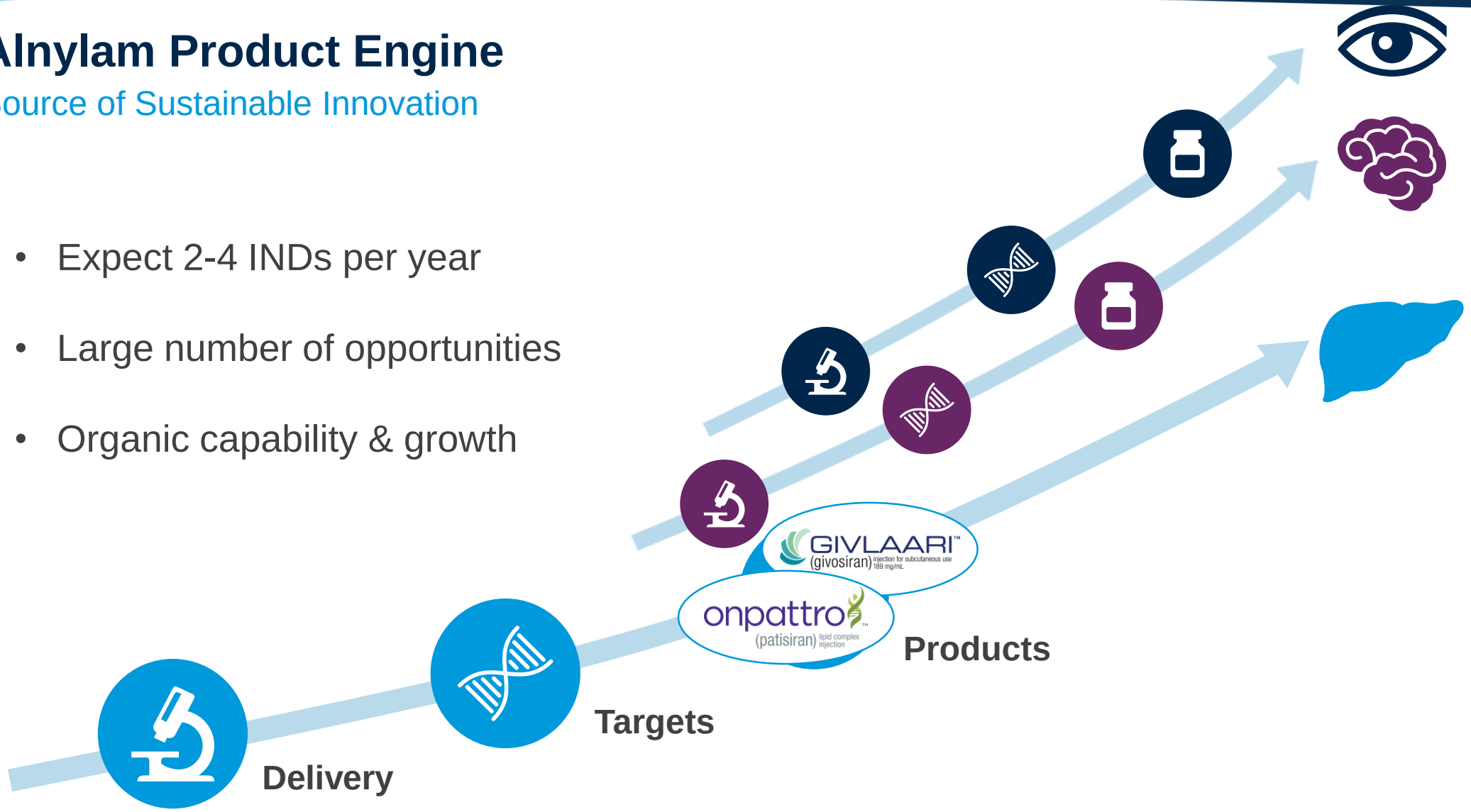
Akshay Vaishnaw, M.D., Ph.D.
President, Research & Development

Alnylam® PHARMACEUTICALS

Alnylam Product Engine

Source of Sustainable Innovation

- Expect 2-4 INDs per year
- Large number of opportunities
- Organic capability & growth



Robust Next Wave Pipeline: 2-4 INDs/Year on Average Planned Through 2025

LIVER

Alnylam
- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

Alnylam/Regeneron
- ALN-HSD
- ALN-REGN1
- ALN-REGN2

Alnylam/Vir
- ALN-VIR2

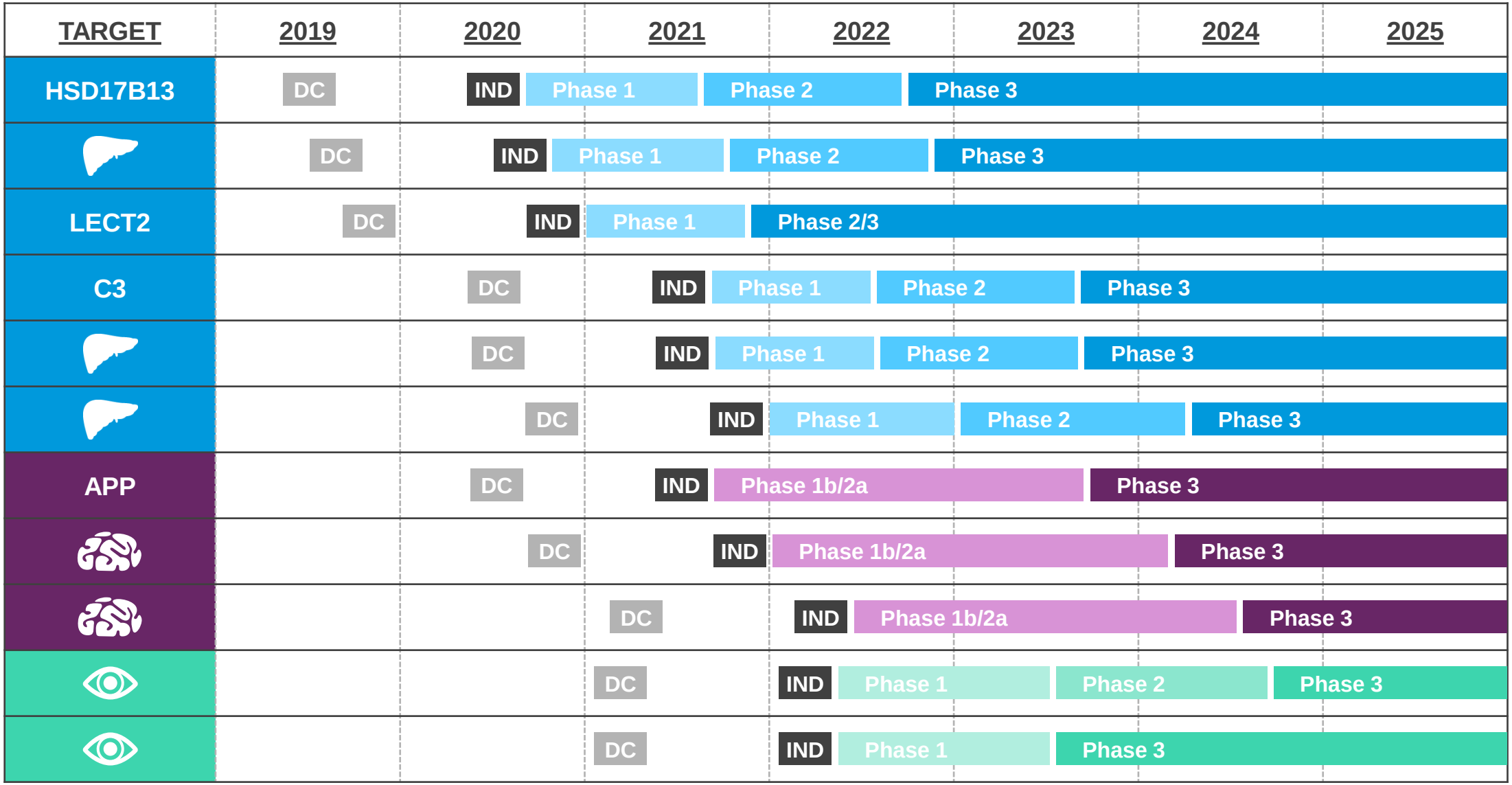
CNS

Alnylam/Regeneron
- ALN-APP
- ALN-HTT
- ALN-REGN3

EYE

Alnylam/Regeneron
- ALN-REGN4
- ALN-REGN5

Illustrative Flow of Potential Next Wave INDs (2020-2022)

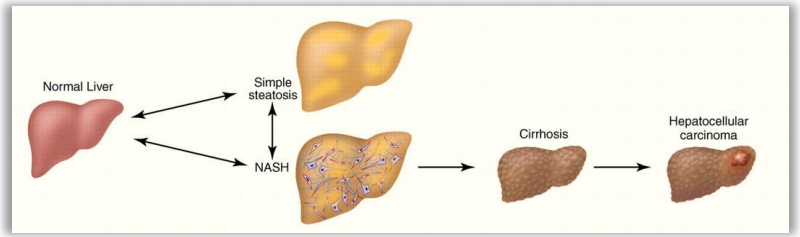


Note: Timing and length of clinical studies are estimates for illustrative purposes

HSD17B13 for NASH

DESCRIPTION

Progressive disease characterized by hepatic fat buildup, inflammation with potential for cirrhosis and liver cancer.



BURDEN

NASH is predicted to be ***the*** major driver for liver transplantation by 2020. Liver-related mortality increases exponentially with fibrosis progression.

TOTAL NASH PATIENT POPULATION

>16 million
adults in U.S.

NASH PATIENTS W/ ADVANCED FIBROSIS (F2-F4)

>6 million
adults in U.S.

TARGET IDENTIFICATION

- Regeneron discovered loss-of-function mutation in the HSD17B13 gene strongly associated with protection against NASH and other chronic liver diseases.
- HSD17B13 is intracellular protein mainly expressed in hepatocytes.

THERAPEUTIC HYPOTHESIS

RNAi-mediated suppression of HSD17B13 will prevent progression to cirrhosis and end-stage liver disease.

OPPORTUNITY

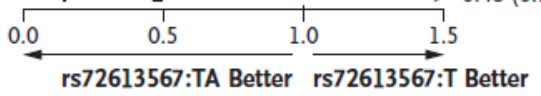
- Develop best-in-class, long-acting, disease-modifying treatment for NASH.
- Foundational template for combination therapy using RNAi therapeutics.

HSD17B13

Identification of a Loss-of-Function Mutation that Protects Against NASH

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)		



Chronic liver diseases with high unmet need

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

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

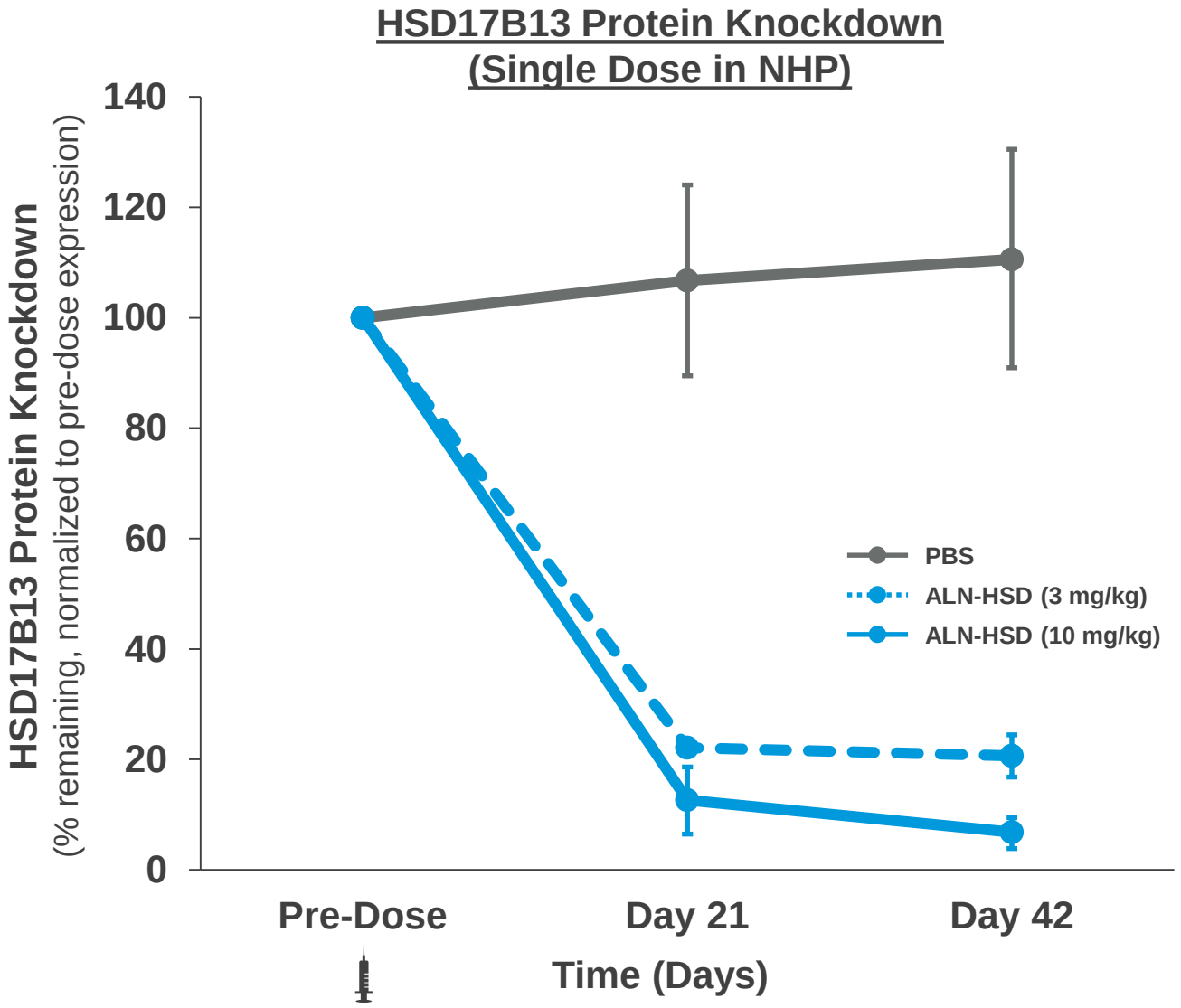
ALN-HSD

- Max knockdown achieved >90%
- Potential for quarterly or bi-annual dosing

[1] Abul-Husn et al. NEJM 2018 378;12, 1096

[2] Estes et al. Hepatology. 2018;67(1):123

HSD17B13 Program Status



ALN-HSD

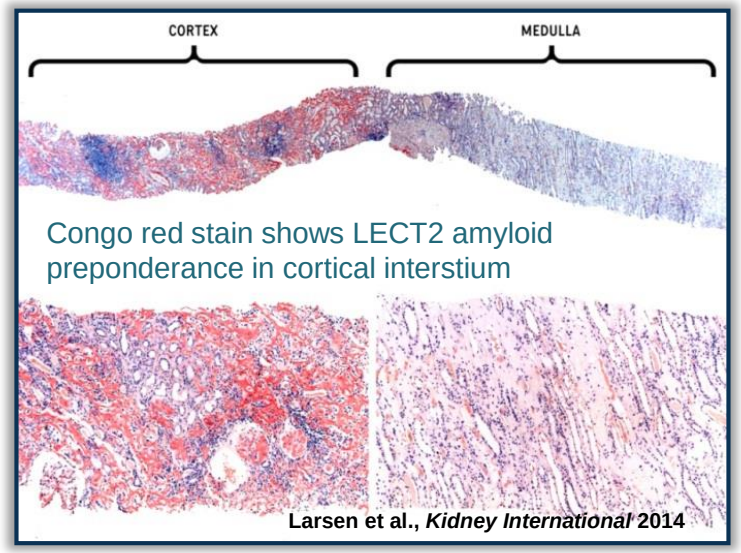
ONGOING WORK & TIMELINES

- IND-enabling studies ongoing
- Planned IND filing in 2020

LECT2 for Newly Described Type of Orphan Renal Amyloidosis

DESCRIPTION

Patients present with chronic progressive kidney disease.



BURDEN

- 90% of U.S. cases are of Mexican ancestry.
- LECT2 may be most common form of renal amyloid in that population.

TARGET IDENTIFICATION

- Recent description of a new form of amyloidosis caused by a protein secreted from the liver.
- Mutations appear to make protein more unstable.
- Upregulation of LECT2 liver expression in the diseased state.

THERAPEUTIC HYPOTHESIS

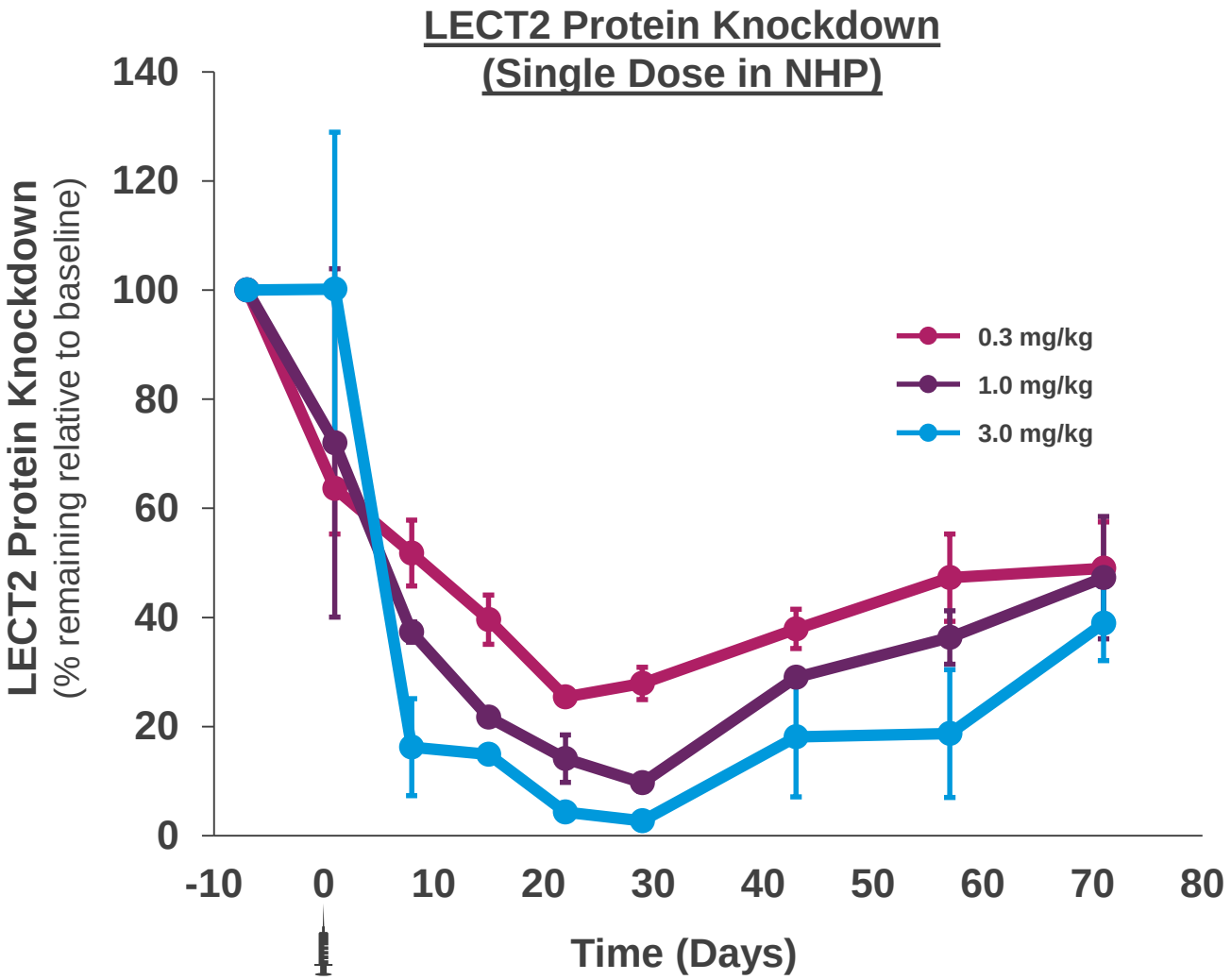
RNAi-mediated suppression of LECT2 production by the liver will stabilize or improve kidney disease caused by renal ALECT2 deposition.

OPPORTUNITY

Application of Alnylam's proven treatment approach for hepatic derived kidney amyloid disease with no existing disease-modifying treatment.

LECT2 Program Status

ALN-LEC Development Candidate (DC) Identified



ALN-LEC

ONGOING WORK & TIMELINES

- IND-enabling studies ongoing
- Planned IND filing in late 2020

C3 for Range of Complement Indications

KIDNEY DISORDERS

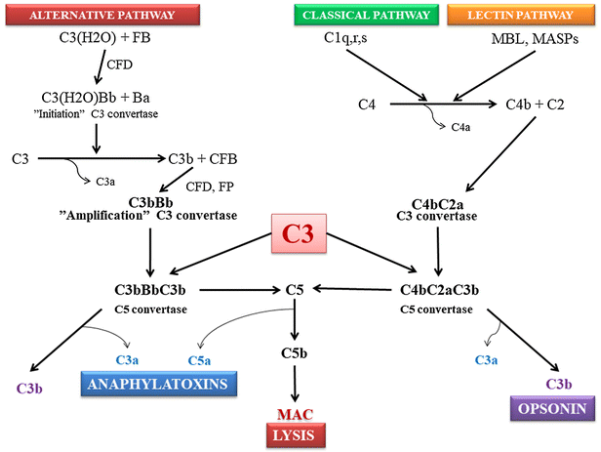
C3 glomerulopathy, lupus nephritis, IgA nephropathy, diabetic nephropathy, and others.

BLISTERING AUTOIMMUNE DISORDERS

Bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus.

AUTOIMMUNE DEMYELINATING PNs

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), Guillain-Barré Syndrome (GBS)



TARGET/INDICATION SELECTION

Known complement involvement in 40+ distinct disorders positions central component C3 for long-duration siRNA therapeutic, to benefit multiple indications including autoimmune anemias, kidney diseases, autoimmune skin blistering disorders, autoimmune myopathies and neuropathies, etc.

THERAPEUTIC HYPOTHESIS

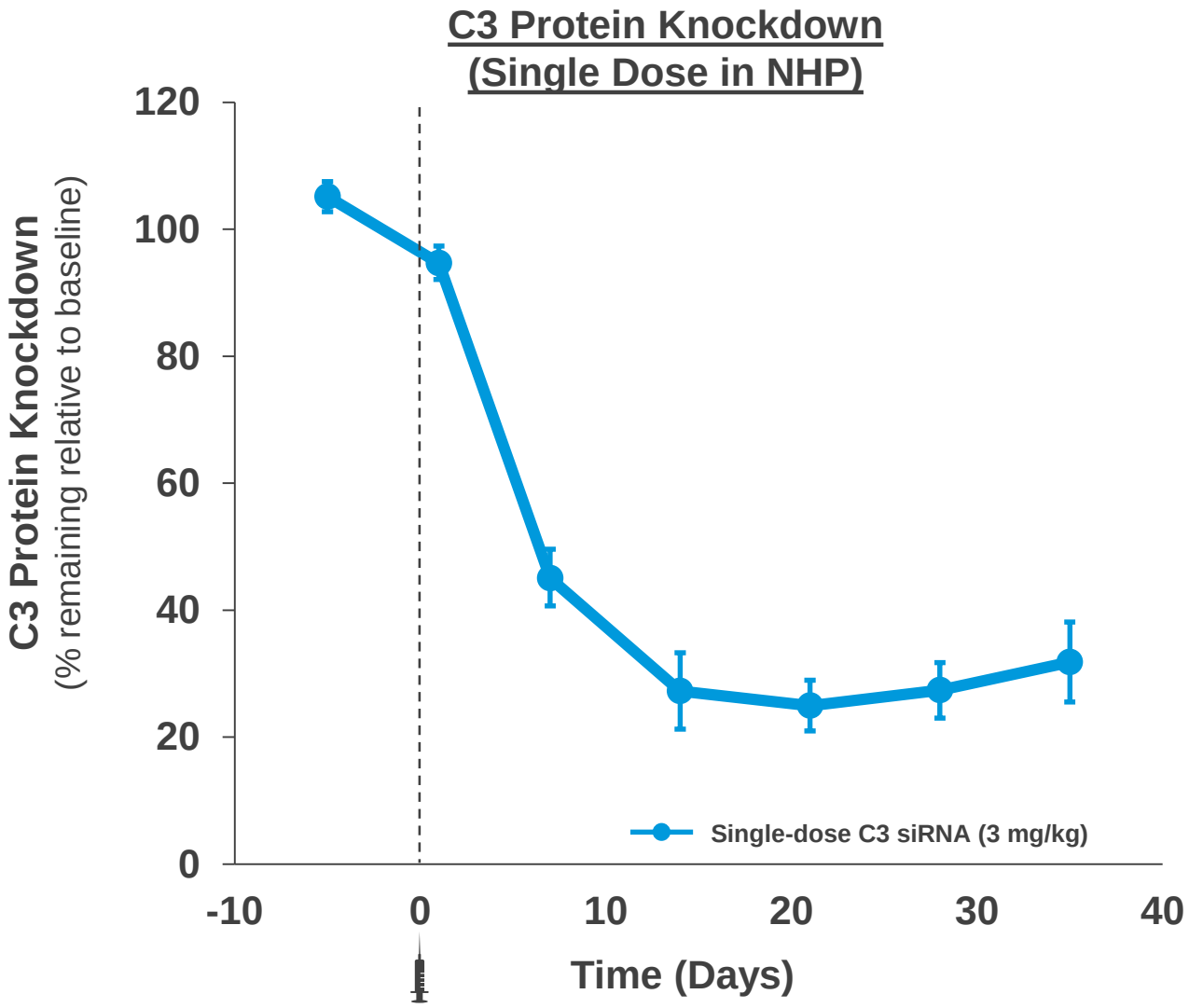
- C3 primarily derived from liver.
- Significant depletion of C3 via siRNA will stably suppress complement-induced inflammation and cell lysis.
- Liver suppression of C3 will not affect C3 produced by bone marrow-derived cells, preserving ability to mount immune responses.

OPPORTUNITY

- C3 opens range of potential indications beyond MAC formation or individually targeting classical, lectin, or alternative complement pathways.
- Durability of subcutaneously-delivered C3 siRNA will have an advantage in chronic disorders.

C3 Program Status

Ongoing Lead Identification for ALN-CC3



ALN-CC3

ONGOING WORK & TIMELINES

- Lead identification ongoing
- DC expected in mid-2020

Robust Next Wave Pipeline: 2-4 INDs/Year on Average Planned Through 2025

LIVER

Alnylam
- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

Alnylam/Regeneron
- ALN-HSD
- ALN-REGN1
- ALN-REGN2

Alnylam/Vir
- ALN-VIR2

CNS

Alnylam/Regeneron
- ALN-APP
- ALN-HTT
- ALN-REGN3

EYE

Alnylam/Regeneron
- ALN-REGN4
- ALN-REGN5

RNAi Therapeutics for CNS Diseases

No Current Therapies to Prevent or Restore Neurodegenerative Disease

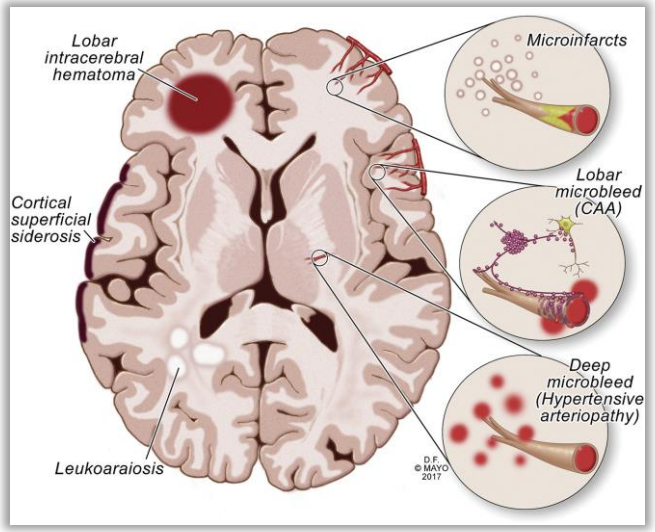
- Dominantly inherited neurodegenerative diseases include
  - Alzheimer's disease
  - Amyotrophic lateral sclerosis (ALS)
  - Frontotemporal dementia
  - Huntington's disease
  - Parkinson's disease
  - Prion disease
  - Spinocerebellar ataxia
  - Many other orphan genetic diseases with CNS component

- 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
- Based on pre-clinical studies, expect superior potency, duration and systemic safety profile vs. ASOs

APP Targeting for Hereditary Cerebral Amyloid Angiopathy (hCAA)

hCAA

Patients present with stroke-like presentation (intracerebral hemorrhage).



BURDEN

- 100% of affected individuals share a common ancestor from the Netherlands.
- Mean age of onset 54 years.

TARGET IDENTIFICATION

- Missense substitution in *APP* (p.Glu693Gln) increases production of Aß40 and causes 100% of known cases of Dutch-type cerebral amyloid angiopathy.
- Autosomal dominant, 100% penetrant genetic syndrome.

THERAPEUTIC HYPOTHESIS

- Aß40 is made in neurons but then undergoes extracellular transit before deposition in the perivascular space.
- RNAi-mediated knockdown of *APP* transcript in neurons will lower production of Aß40, halting toxic protein build-up.

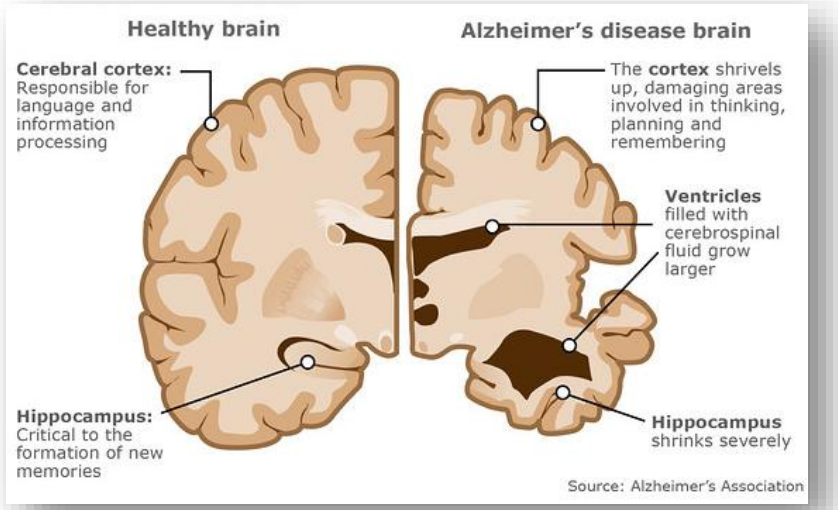
OPPORTUNITY

- Application of Alnylam's CNS platform to reduce perivascular *APP*-derived amyloid with no existing disease-modifying treatment.
- Potential for expansion into sporadic CAA, a very common age-related cause of common hemorrhagic stroke.

APP Targeting for Early Onset Familial Alzheimer's Disease (EOFAD)

EOFAD

Patients develop rapidly progressive Alzheimer's-type dementia.



BURDEN

- ~50,000 affected globally.
- Mean age of onset 44 years with rapid progression over 6-8 years.

TARGET IDENTIFICATION

- Exclusively caused by mutations in genes that regulate *APP* protein metabolism (*APP*, *PSEN1*, *PSEN2*) by increasing production of Aß42.
- Autosomal dominant, 100% penetrant genetic syndrome.

THERAPEUTIC HYPOTHESIS

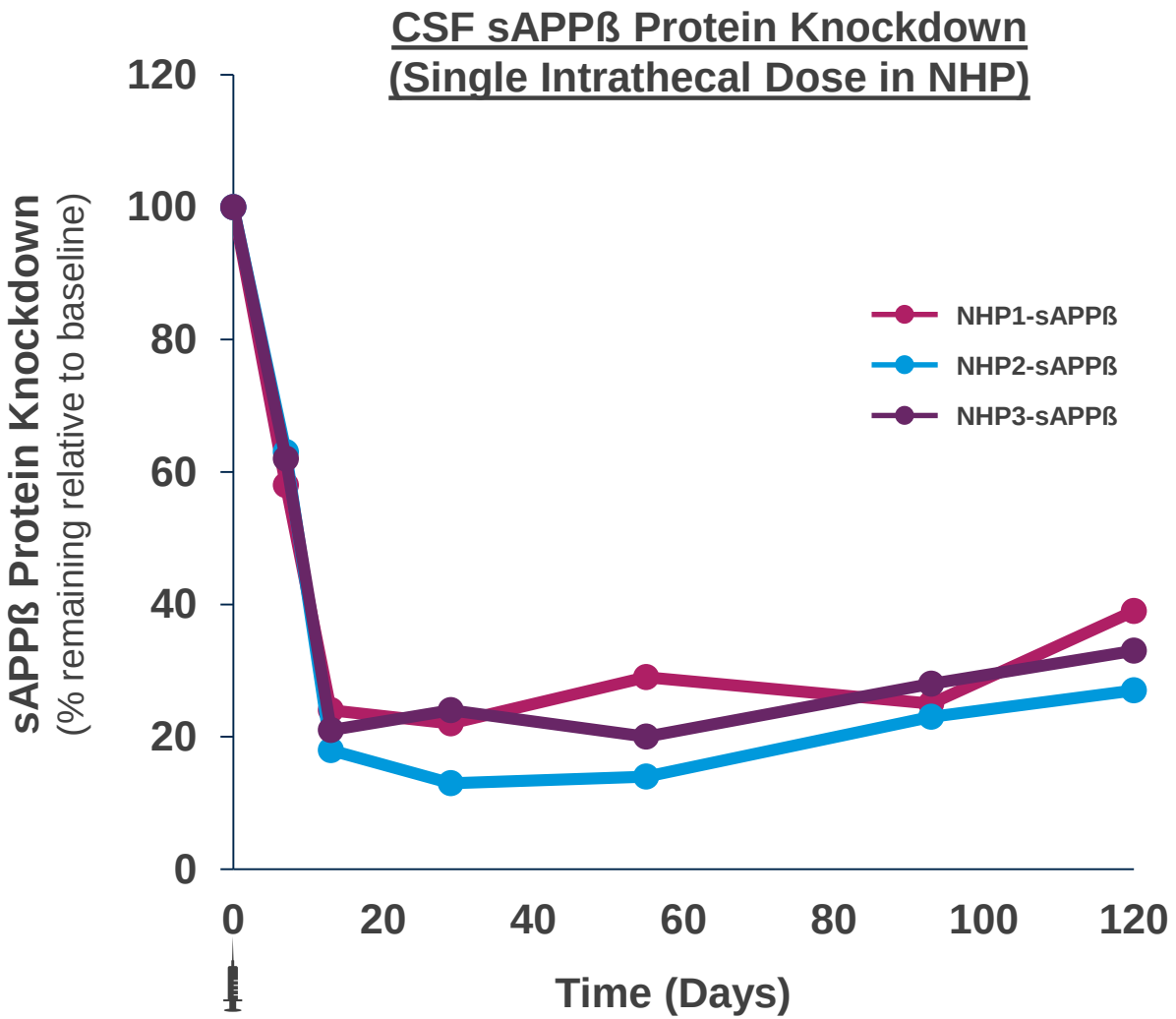
- Aß42 is made in neurons and aggregates in the intracellular and extracellular brain parenchyma.
- RNAi-mediated knockdown of *APP* transcript in neurons will lower production of Aß42, halting aggregation and plaque formation.

OPPORTUNITY

- Application of Alnylam's CNS platform to reduce parenchymal *APP*-derived amyloid with no existing disease-modifying treatment.
- Potential for expansion into sporadic Alzheimer's disease.

APP Program Status

ALN-APP: Advanced Preclinical Program



ALN-APP

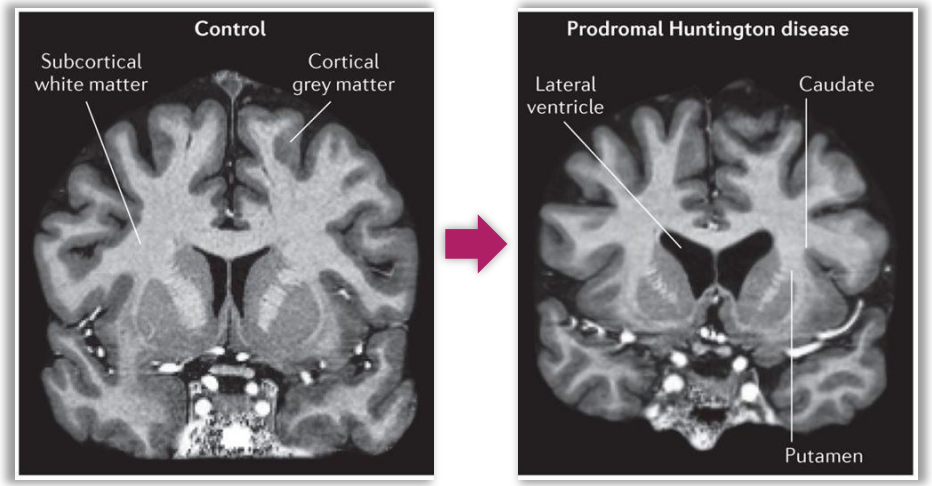
ONGOING WORK & TIMELINES

- Finalize DC selection
- Planned IND filing in mid-2021

HTT Targeting for Early Manifest Huntington's Disease

HTT

Patients present with progressive motor, cognitive and psychiatric decline.



BURDEN

- Affecting ~30,000 in U.S. with disease duration of 15-20 years.

TARGET IDENTIFICATION

- Autosomal dominant, gain-of-function genetic disease.
- 100% age-related penetrance.
- Trinucleotide repeat expansion in exon 1 of the huntington gene (*HTT*).

THERAPEUTIC HYPOTHESIS

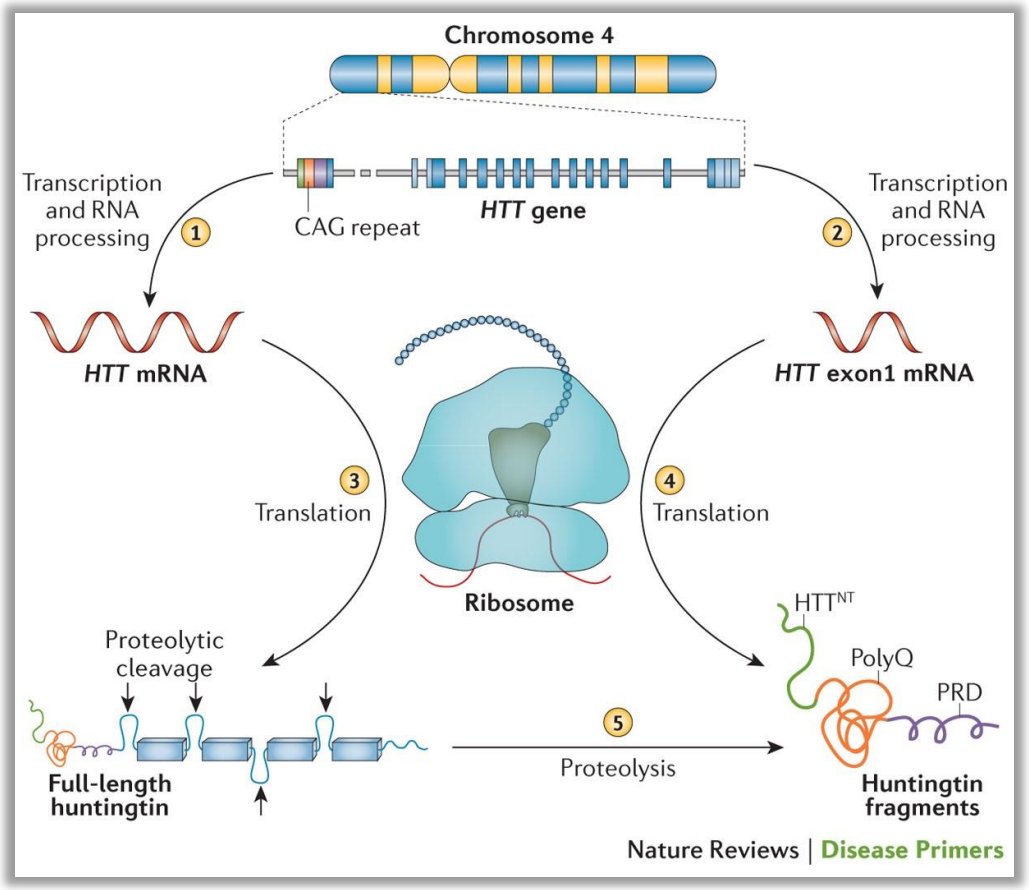
- RNAi-mediated knockdown of *HTT* transcript in neurons will reduce both RNA-induced and protein-induced neuronal toxicity, halting disease progression.

OPPORTUNITY

- Application of Alnylam's CNS platform to develop a therapeutic for a devastating progressive neurodegenerative condition.
- Potential differentiation over competition via exon 1 targeting strategy, targeting a pathogenic isoform that contributes to disease progression.

HTT Program Status

ALN-HTT: Advanced Preclinical Program



ALN-HTT

ONGOING WORK & TIMELINES

- Finalize DC selection
- Advance toward IND

Tabrizi, S. J. et al. (2015) Huntington disease. Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.5

Robust Next Wave Pipeline: 2-4 INDs/Year on Average Planned Through 2025

LIVER

Alnylam
- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

Alnylam/Regeneron
- ALN-HSD
- ALN-REGN1
- ALN-REGN2

Alnylam/Vir
- ALN-VIR2

CNS

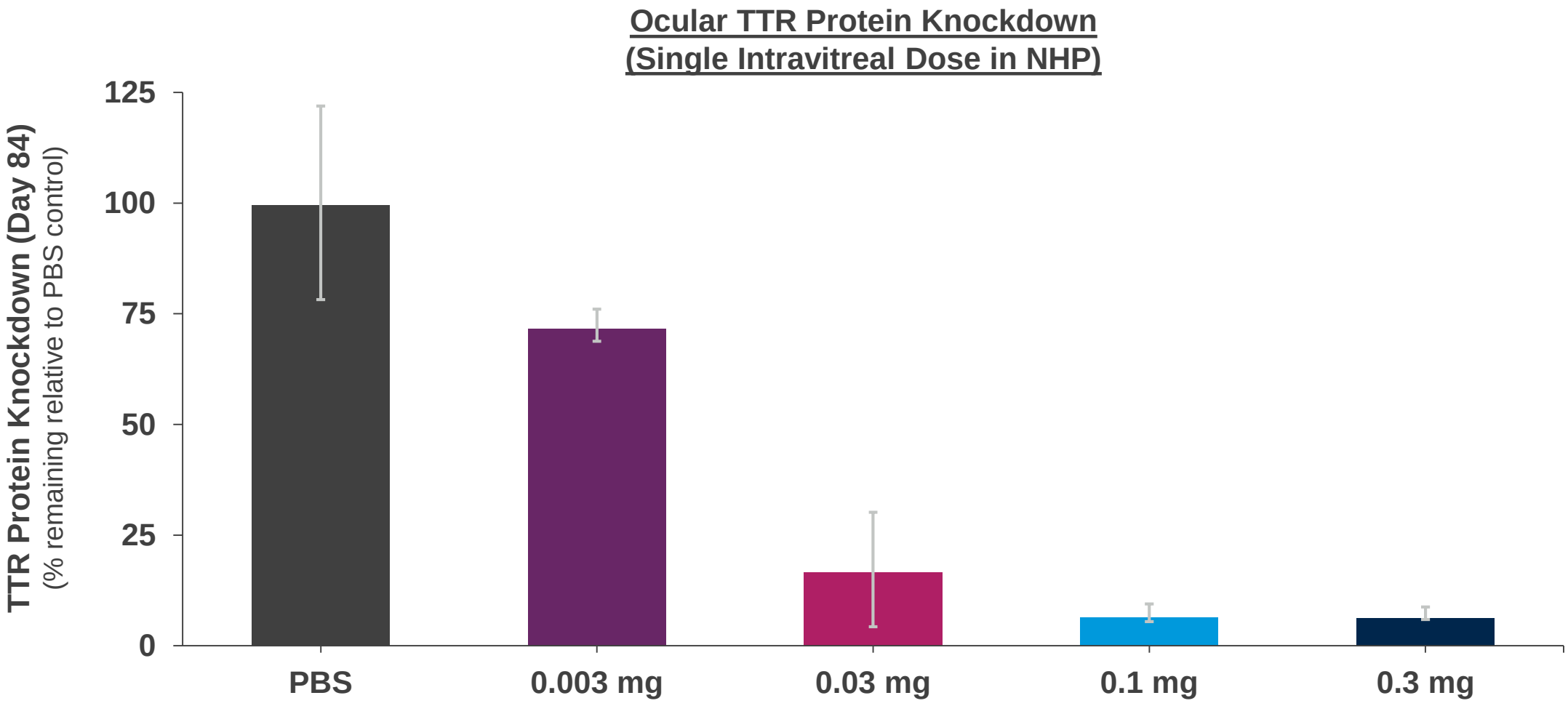
Alnylam/Regeneron
- ALN-APP
- ALN-HTT
- ALN-REGN3

EYE

Alnylam/Regeneron
- ALN-REGN4
- ALN-REGN5

Ocular Update

Ocular NHP Potency with Potential for Infrequent Dosing with Low ug Doses per Eye



Pipeline Growth Summary

Alnylam has built industry-leading pipeline of innovative medicines

- 100% organic platform for self-sustainable cycle of success
- To date, >50% cumulative probability of success from FIH to positive Phase 3

Alnylam R&D strategy validated by pipeline productivity originally guided in Jan 2016

- Expect to exceed 2020 goal of 3 approved RNAi therapeutics

Strategic evolution of clinical-stage portfolio with industry-leading, safe, potent and highly durable RNAi therapeutics

- Continued growth in key late-stage programs (e.g., TTR) and novel liver targets
- Addition of new therapeutic areas: CNS and ocular
- Increasing balance between orphan and large market opportunities (ATTR, hypertension, NASH, HBV, EOFAD/Alzheimer's, CAA)

Future outlook

- Continued output of 2-4 INDs per year of RNAi therapeutics across liver, CNS and ocular pipelines
- Focus on genetic validation to enhance probability of success
- Platform innovation promises new opportunities (e.g., bispecific, oral)

Roadmap to Self-Sustainability

Jeff Poulton
Chief Financial Officer

Alnylam® PHARMACEUTICALS

Path to Self-Sustainability

Becoming a profitable, self-sustainable company is a top Alnylam priority

Focused on key levers affecting pathway to planned profitability

- Topline growth
  - Near-term revenue growth by optimizing rapid succession of product launches (peers often take many years to get to second launch)
  - Meaningful royalty revenue potential from partnered assets in large indications
  - Collaboration revenues from strategic partnerships
  - Long-term growth by advancing mid and early-stage pipeline
- Disciplined investment
  - Continue to invest in proven organic R&D platform to drive long-term topline growth with significant investment in late stage programs
  - Continue to leverage strategic partnerships to drive R&D innovation while sharing in costs & risk
  - Disciplined SG&A investment, leveraging ONPATTRO® (patisiran) commercial infrastructure to support future launches

The path to financial self-sustainability begins now

- We project 2019 will be our peak non-GAAP net operating loss year

Potential Topline Drivers of Growth Through 2025

Analyst Revenue Projections ($M)

VUTRISIRAN

FITUSIRAN (ROYALTIES)

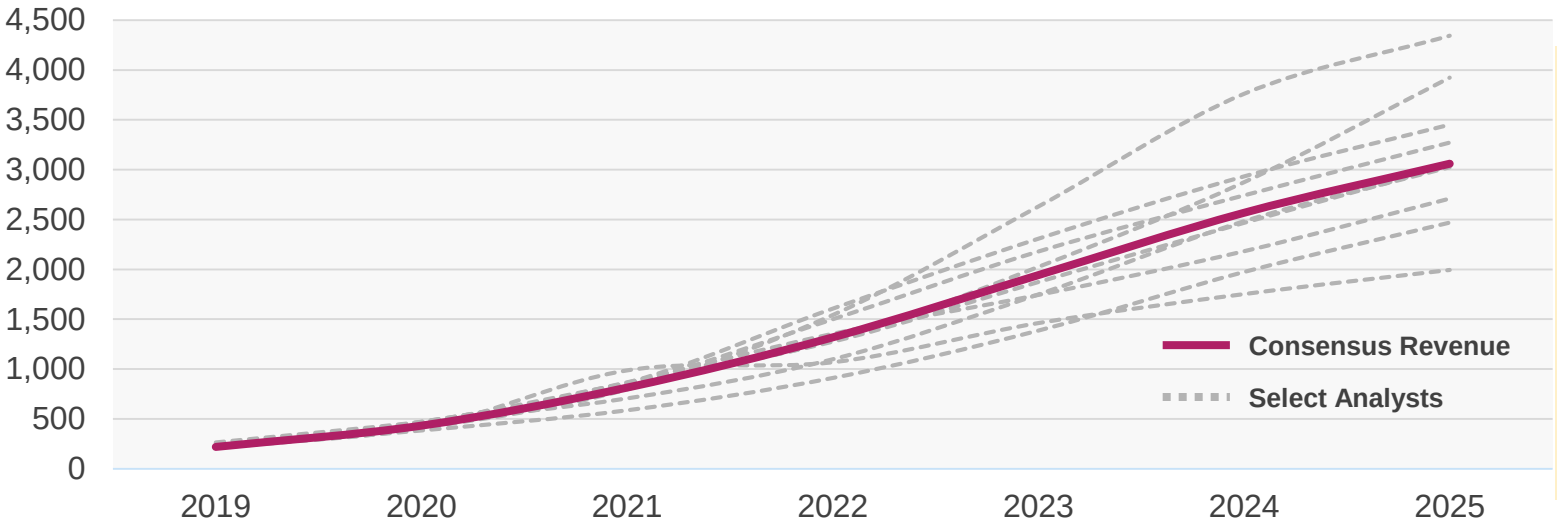
LUMASIRAN

INCLISIRAN (ROYALTIES)

GIVLAARI™ (givosiran)

ONPATTRO® (patisiran)

COLLABORATIONS



+ Cemdisiran (mono & combo)

+ AAT02

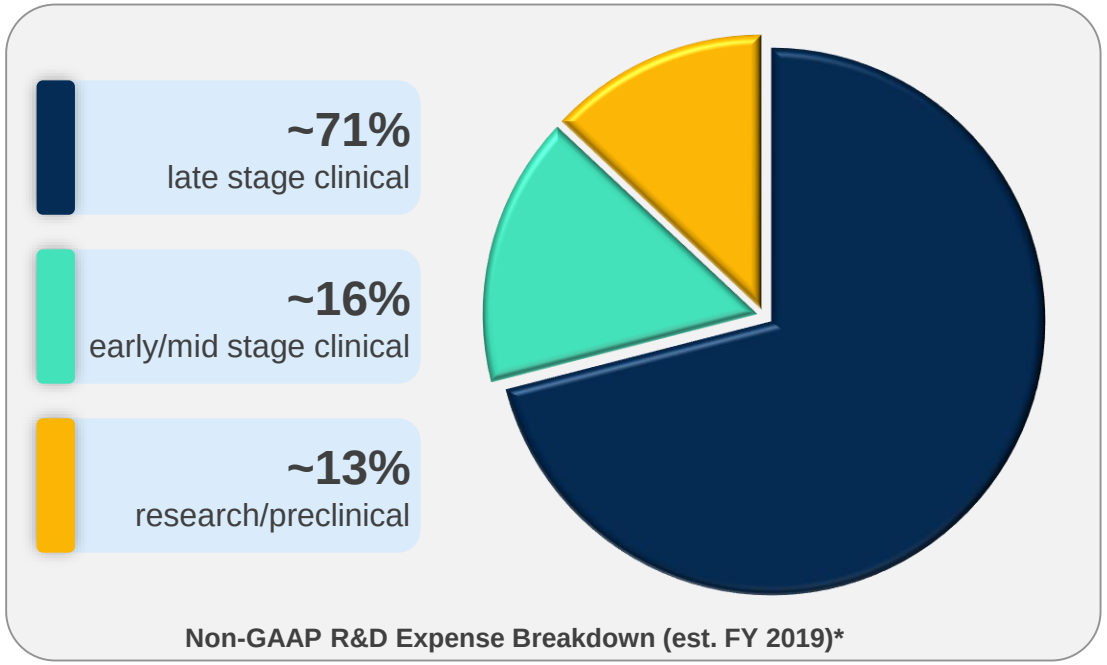
+ HBV02

+ AGT

+ 2-4 INDs per year

Investing in a Sustainable Business

Supporting Near and Long-Term Topline Growth on the Path Toward Profitability



Non-GAAP R&D Expense Breakdown (est. FY 2019)*

R&D investment drives sustainable long-term growth

- Revenue growth from potential 'second wave' of approved RNAi therapeutics to come from current R&D spend
  - Better than industry average probability of success supports increasing platform investment
  - Indication diversity in both rare and common disease populations creates attractive long-term growth potential
  - Expanding beyond the liver into ocular and CNS targets via collaboration with Regeneron

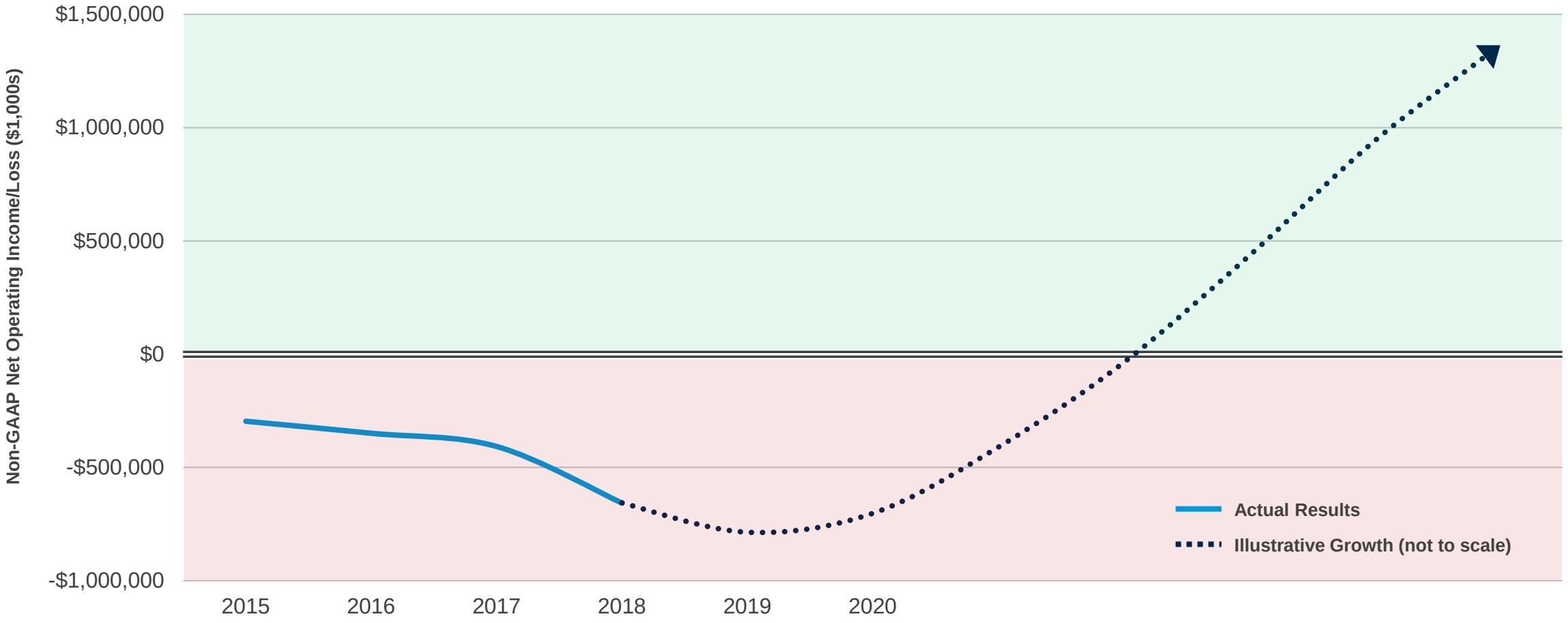
SG&A expense discipline to maximize value

- Ensure operational excellence commercializing wholly-owned programs
  - Global footprint with presence in multiple regions, established with first product and leverageable for subsequent products
  - Capitalize on cross-therapeutic area/product synergies
  - Maintain lean corporate G&A infrastructure to support business

* Internal estimate consistent with previously issued guidance on aggregate non-GAAP R&D expenses for 2019

Entering the Era of Projected Growth

2019 Expected to be Peak Non-GAAP Net Operating Loss Year



	2015	2016	2017	2018	2019	2020
# Late Stage Programs:	2	1	4	6	6	6
# Commercial Products:	0	0	0	1	2	4

Q&A Session #2

12:10 – 12:30 PM

Moderator:

- Yvonne Greenstreet, Chief Operating Officer

Panelists:

- Pritesh J. Gandhi, PharmD., VP & General Manager, Lumasiran
- Akshay Vaishnaw, M.D., Ph.D., President, Research & Development
- Jeff Poulton, Chief Financial Officer

Closing Statements

- Industry-leading pipeline of innovative medicines now with two approved RNAi therapeutics
- Substantial opportunity in TTR with market-leading programs
  - Ongoing clinical studies address full spectrum of disease, including ATTR amyloidosis with cardiomyopathy
- By 2020, on track for 4 marketed products, 14 organic clinical stage programs, 6 late-stage development programs, across 4 STArs
- Unparalleled product engine capable of producing 2-4 new INDs annually
- Progressing toward self-sustainable financial profile for future growth and value creation

AT OUR CORE… PATIENTS

Why We Do What We Do!

Mayah, living with PH1 (USA)

Veronika, living with porphyria (Spain)

David, living with hATTR amyloidosis (Canada)

The Skinner Family, three of four children living with PH1 (USA)

Colin, living with porphyria (USA)

CeCe, Living with hATTR amyloidosis (USA)

Alnylam® PHARMACEUTICALS