Alnylam R&D Day 2020

Day 1

December 15, 2020

Alnylam PHARMACEUTICALS

Agenda

Timing	Topic	Speaker
9:00 – 9:05 a.m. ET	**Welcome**	Christine Lindenboom *SVP, Investor Relations and Corporate Communications*
9:05 – 9:10	**Building a Leading Biopharmaceutical Company**	John Maraganore, Ph.D. *Chief Executive Officer*
9:10 – 9:30	**Bringing RNAi Therapeutics to Patients Around the World**	Yvonne Greenstreet, MBChB, MBA *President and Chief Operating Officer*
9:30 – 9:50	**Delivering Sustainable Innovation with RNAi Therapeutics**	Akshay Vaishnaw, M.D., Ph.D. *President, R&D*
9:50 – 10:00	**Break**	
10:00 – 10:40	**Expanding Alnylam TTR Franchise into Wild-Type ATTR Amyloidosis**	Philip Hawkins, FRCP, FRCPath, FMedSci *National Amyloidosis Centre, Royal Free Hospital and University College London, UK* John Vest, M.D. *VP, Clinical Research*
10:40 – 11:20	**Reimagining the Treatment of Hypertension with ALN-AGT**	Akshay Desai, M.D., M.P.H. *Brigham and Women's Hospital, Harvard Medical School* Lauren Melton *Senior Director, Program Leader ALN-AGT*
11:20 a.m. – 12:00 p.m.	**Q&A**	All

Reminders

- Event scheduled to end ~12:00 p.m. ET.
- Moderated Q&A session at the conclusion of the presentations.
- To submit a question, type your question in the ‘Ask a Question’ field.
- Replay will be available on Investors page of our website later today.

Forward Looking Statements, Non-GAAP Financial Measures & Other Notices

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by our products, or in patient enrollment in clinical trials, potential supply chain disruptions, and other potential impacts to our business, the effectiveness or timeliness of steps taken by us to mitigate the impact of the pandemic, and our ability to execute business continuity plans to address disruptions caused by the COVID-19 or any future pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates, including patisiran, vutrisiran, cemdisiran, ALN-AGT, ALN-HSD, ALN-APP, ALN-AAT02, ALN-HBV02,–ALN-COV, ALN-XDH and ALN-KHK; 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 and our marketed products, including ONPATTRO® (patisiran), GIVLAARI® (givosiran), OXLUMO™ (lumasiran), inclisiran and vutrisiran; intellectual property matters including potential patent litigation relating to our platform, products or product candidates; our and our partner's ability to obtain regulatory approval for our product candidates, including inclisiran, and our ability to maintain regulatory approval and obtain pricing and reimbursement for products, including ONPATTRO, GIVLAARI and OXLUMO; our ability to successfully launch, market and sell our approved products globally, including ONPATTRO, GIVLAARI and OXLUMO, and achieve net product revenues for ONPATTRO within our further revised expected range during 2020; our ability to successfully expand the indication for ONPATTRO in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses within the reduced ranges of guidance provided by us through implementation of further discipline in operations to moderate spend and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to establish and maintain business alliances; our dependence on third parties, including Novartis, for the development, manufacture and commercialization of inclisiran, Regeneron, for development, manufacture and commercialization of certain products, including eye and CNS products such as ALN-APP, and Vir for the development of ALN-HBV02 and ALN-COV and other potential RNAi therapeutics targeting SARS-CoV-2 and host factors for SARS-CoV-2; the outcome of litigation; and the risk of government investigations; as well as those risks and other factors more fully discussed in our most recent annual, quarterly and current reports filed with the SEC. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements. Today's discussions and presentations are for the investor community only, and are not intended to promote any Alnylam products or product candidates or to influence any prescription, recommendation or use of Alnylam products. All trademarks in today's presentations are the property of their respective owners.

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 expenses, unrealized gain on marketable equity securities, costs associated with our strategic financing collaboration, loss on contractual settlement and change in estimate of contingent liabilities. 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 unrealized gain on marketable equity securities, costs associated with our strategic financing collaboration, loss on contractual settlement and change in estimate of contingent liabilities because the Company believes these items are non-recurring transactions outside the ordinary course of the Company's business.

Acknowledgments and Disclosures

All speakers are employees of Alnylam Pharmaceuticals except for Dr. Akshay Desai, Professor Philip Hawkins and Dr. Arun Sanyal, who are paid consultants to Alnylam. Alnylam Pharmaceuticals and the speakers at this event wish to thank patients, families, caregivers and dedicated researchers at their affiliated as well as other entities for their contributions to the findings presented.

VOICES OF **PATIENTS & CAREGIVERS**

“Over the course of a year, as a result of having no attacks, I didn’t take a single sick day from work.”

Lina, GIVLAARI patient ambassador

Alnylam® PHARMACEUTICALS

Building a Leading Biopharmaceutical Company

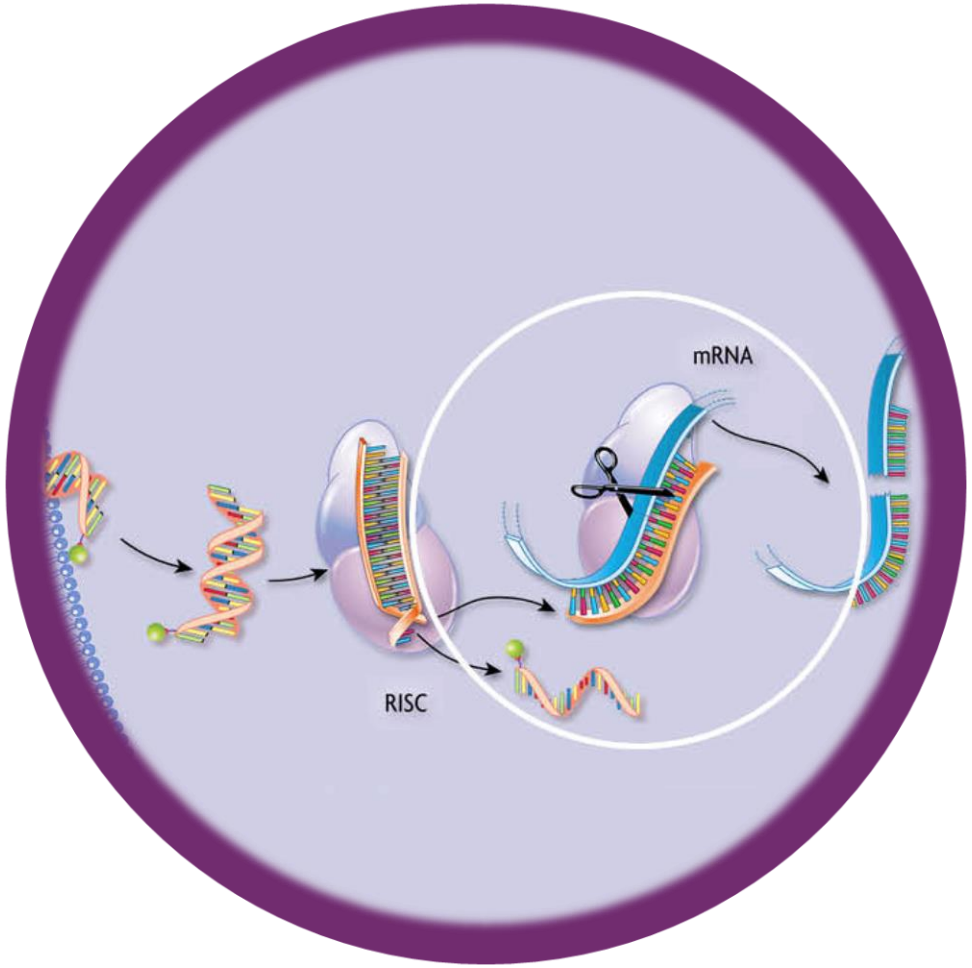
John Maraganore, Ph.D.
Chief Executive Officer

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



Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

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

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 4)*	REGISTRATION/ COMMERCIAL[1]	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Patisiran	*ATTR Amyloidosis*		●		Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*		●		15-30% Royalties
Vutrisiran	*ATTR Amyloidosis*		●		Global
Lumasiran	*Recurrent Renal Stones*	●			Global
Cemdisiran	*Complement-Mediated Diseases*	●			50-50
Cemdisiran/Pozelimab Combo[6]	*Complement-Mediated Diseases*	●			Milestone/Royalty
ALN-AAT02 (DCR-A1AT)[7]	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
ALN-AGT	*Hypertension*	●			Global
ALN-HSD	*NASH*	●			Milestone/Royalty

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S. and EU for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development

As of December 2020

The first RNAi therapeutic is

APPROVED IN U.S., EU, CANADA, JAPAN, SWITZERLAND, BRAZIL & ISRAEL

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

onpattro®
(patisirana) solução para infusão intravenosa

The second RNAi therapeutic is

APPROVED IN THE U.S., EU, BRAZIL & CANADA

The third RNAi therapeutic is

NOW APPROVED IN THE EU & U.S.

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

NOVARTIS

Novartis receives EU approval for Leqvio®* (inclisiran), a first-in-class siRNA to lower cholesterol with two doses a year**

Dec 11, 2020

* Product and brand name are currently under FDA review.
** After an initial dose and one at 3 months.


Alnylam®
PHARMACEUTICALS
2020
3 STArs 4
3 Marketed Products 4
10 Clinical Programs 12
4 Late Stage Programs 6

Two Horizons for Alnylam

Next 1-2 Years

- Growing a Global Commercial Company

Next 3-5 Years

- Building a Top-Five Biotech

Alnylam 2021 Goals

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

		2021*		
		Early	Mid	Late
onpattro® (patisiran) lipid complex injection 10 mg/5 mL (ATTR Amyloidosis)	Global Commercial Execution	●	●	●
	Complete APOLLO-B Phase 3 Enrollment	●		
GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL (Acute Hepatic Porphyria)	Global Commercial Execution	●	●	●
	Japan Approval		●	
OXLUMO™ (lumasiran) for injection 94.5 mg/0.5 mL (Primary Hyperoxaluria Type 1)	Global Commercial Execution	●	●	●
	Brazil Approval	●		
	ILLUMINATE-C Phase 3 Topline		●	
VUTRISIRAN (ATTR Amyloidosis)	HELIOS-A Phase 3 Topline – 9 Month Endpoint	●		
	File NDA	●		
	Initiate q6M Dose Regimen Study	●		
	HELIOS-A Phase 3 Topline – 18 Month Endpoint (incl. cardiac)			●
	HELIOS-B Phase 3 Enrollment	●	●	●
ALN-AGT (Hypertension)	Initiate KARDIA-1 and -2 Phase 2 Studies		●	
ADDITIONAL CLINICAL PROGRAMS	Continue to advance early/mid-stage pipeline; File 2-4 new INDs; Present clinical data	●	●	●
PARTNERED PROGRAMS				
Leqvio® (inclisiran) (Hypercholesterolemia)	Support, as Needed, Global Commercial Execution	●	●	●
	Support, as Needed, ORION-4 CVOT Phase 3 Enrollment	●	●	●
FITUSIRAN (Hemophilia)	Support, as Needed, Sanofi on ATLAS Phase 3 Studies	●	●	●

Alnylam 2021 Goals

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

		2021*		
		Early	Mid	Late
onpattro (patisiran) lipid complex injection 10 mg/5 mL (ATTR Amyloidosis)	Global Commercial Execution	●	●	●
	Complete APOLLO-B Phase 3 Enrollment	●		
GIVLAAR (givosiran) injection for subcut 189 mg/mL (Acute Hepatic Porp			●	●
			●	
OXLUM (lumasiran) for inj 94.5 m (Primary Hyperoxaluria			●	●
			●	
VUTRISIRAN (ATTR Amyloidos				
				●
			●	●
ALN-AGT (Hypertension)			●	
ADDITIONAL CLINICAL PR		●	●	●
PARTNERED PROGRAMS				
Leqvio® (inclisiran) (Hypercholesterolemia)	Support, as Needed, Global Commercial Execution	●	●	●
	Support, as Needed, ORION-4 CVOT Phase 3 Enrollment	●	●	●
FITUSIRAN (Hemophilia)	Support, as Needed, Sanofi on ATLAS Phase 3 Studies	●	●	●

4 commercial brands globally

1 NDA filing (vutrisiran)

2 Phase 3 readouts (vutrisiran, lumasiran)

4 key Phase 3 programs (patisiran, vutrisiran, fitusiran, lumasiran)

2 key Phase 2 programs (cemdisiran, ALN-AGT)

2-4 new INDs

Additional Launches Planned Over Next 18-24 Months

2018	2019	2020	2020	2021-2023	
onpattro® (patisiran) lipid complex injection 10 mg/5 mL	GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL	OXLUMO™ (lumasiran) for injection 94.5 mg/0.5 mL	**Leqvio®** (inclisiran)	**Vutrisiran**	**Fitusiran***
ONPATTRO is indicated in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults[1]	GIVLAARI is indicated in the U.S. for the treatment of adults with acute hepatic porphyria[2]	OXLUMO is indicated in the U.S. for the treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels in pediatric and adult patients[3]	Leqvio is approved in the EU for the treatment of adults with hypercholesterolemia or mixed dyslipidemia[4]	ATTR amyloidosis	Hemophilia
				HELIOS-A Phase 3 topline results expected in early 2021	*Two of three Phase 3 studies fully enrolled*

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

[1] ONPATTRO is approved in U.S. and Canada for the PN of hATTR amyloidosis in adults, and in EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. For additional information on ONPATTRO, see Full Prescribing Information
[2] GIVLAARI is approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older. For additional information on GIVLAARI, see Full Prescribing Information
[3] OXLUMO is approved in the U.S. and EU for the treatment of primary hyperoxaluria type 1 in all age groups. For additional information on OXLUMO, see Full Prescribing Information
[4] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran under a license and collaboration agreement with Alnylam Pharmaceuticals, a leader in RNAi therapeutics
* Sanofi Genzyme is leading and funding development of fitusiran and will commercialize fitusiran, if successful
Anticipated dates of launch based on current development timelines for investigational therapeutics and assuming positive pivotal study data and regulatory approval

Two Horizons for Alnylam

Next 1-2 Years

- Growing a Global Commercial Company

Next 3-5 Years

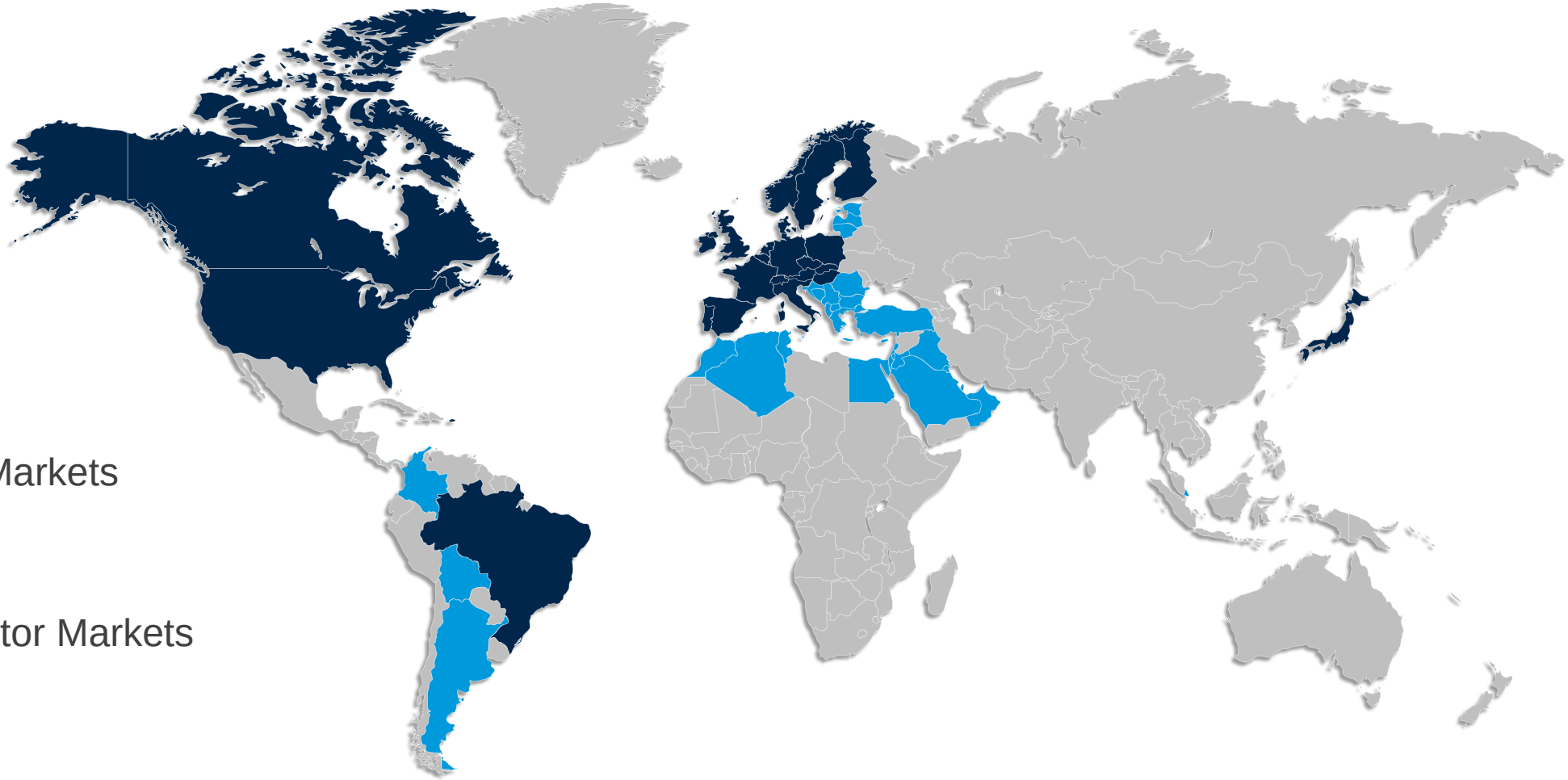
- Building a Top-Five Biotech

1. Continue Global Commercial Execution and Leverage Capabilities

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

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

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

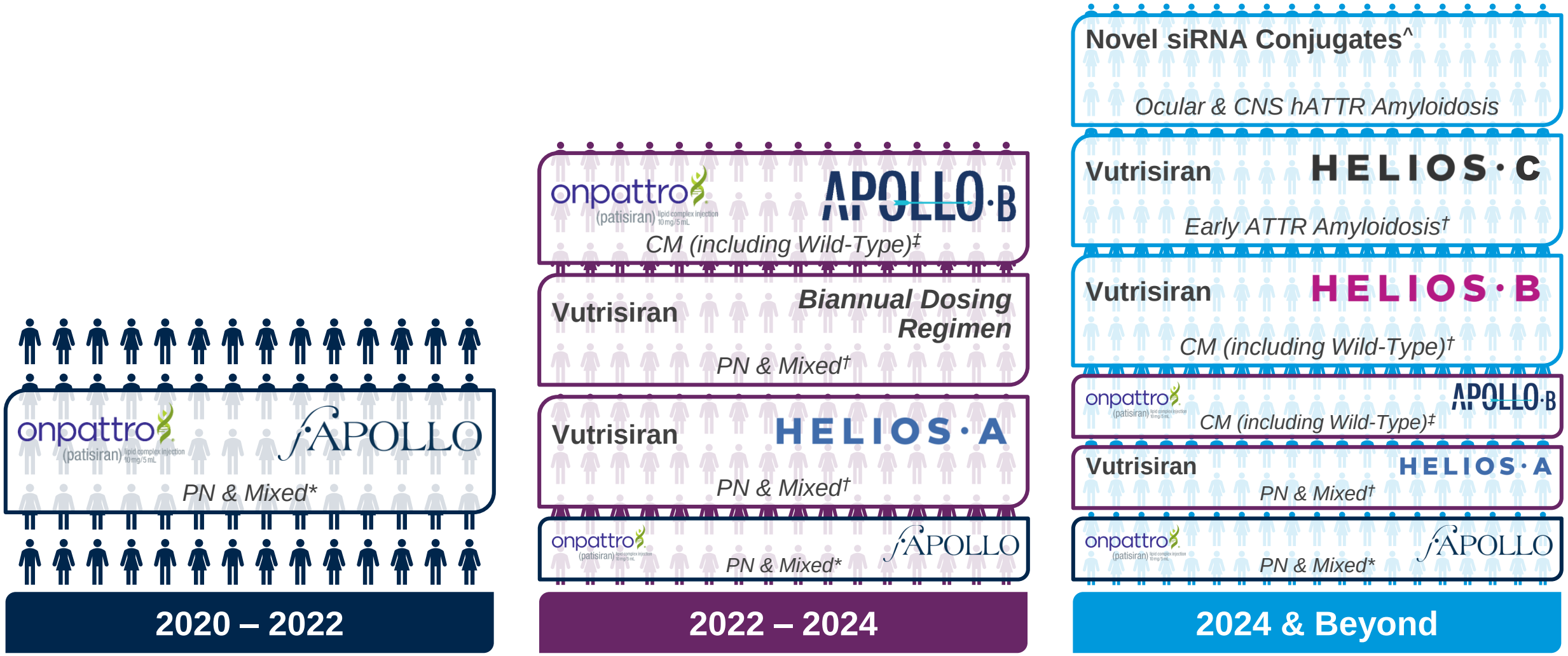


24 Direct Markets

34 Distributor Markets

2. Expand Alnylam ATTR Amyloidosis Franchise

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



* ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; ‡ 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

3. Advance Early/Mid-Stage Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 4)*	REGISTRATION/ COMMERCIAL[1]	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Patisiran	*ATTR Amyloidosis*		●		Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*		●		15-30% Royalties
Vutrisiran	*ATTR Amyloidosis*		●		Global
Lumasiran	*Recurrent Renal Stones*	●			Global
Cemdisiran	*Complement-Mediated Diseases*	●			50-50
Cemdisiran/Pozelimab Combo[6]	*Complement-Mediated Diseases*	●			Milestone/Royalty
ALN-AAT02 (DCR-A1AT)[7]	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
ALN-AGT	*Hypertension*	●			Global
ALN-HSD	*NASH*	●			Milestone/Royalty

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S. and EU for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development

As of December 2020

4. Expand from Rare to Prevalent Diseases

RARE

ONPATTRO-PN
GIVLAARI
OXLUMO
Vutrisiran-PN
Fitusiran
ALN-AAT02
ALN-APP
ALN-HTT

SPECIALTY

ONPATTRO-CM
Vutrisiran-CM
Cemdisiran

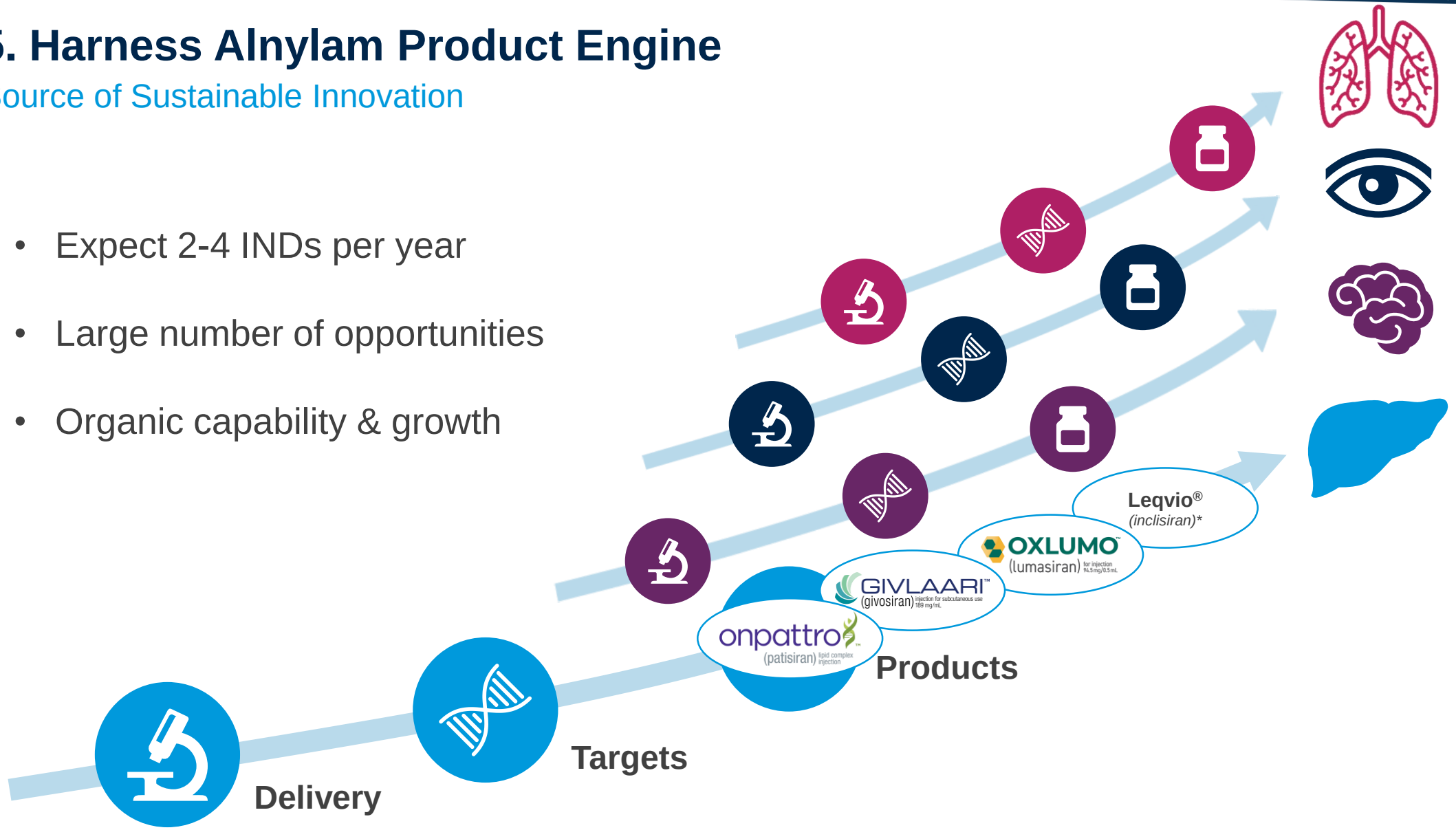
PREVALENT

Leqvio® (inclisiran)
ALN-HBV02 (VIR-2218)
ALN-AGT
ALN-HSD

5. Harness Alnylam Product Engine

Source of Sustainable Innovation

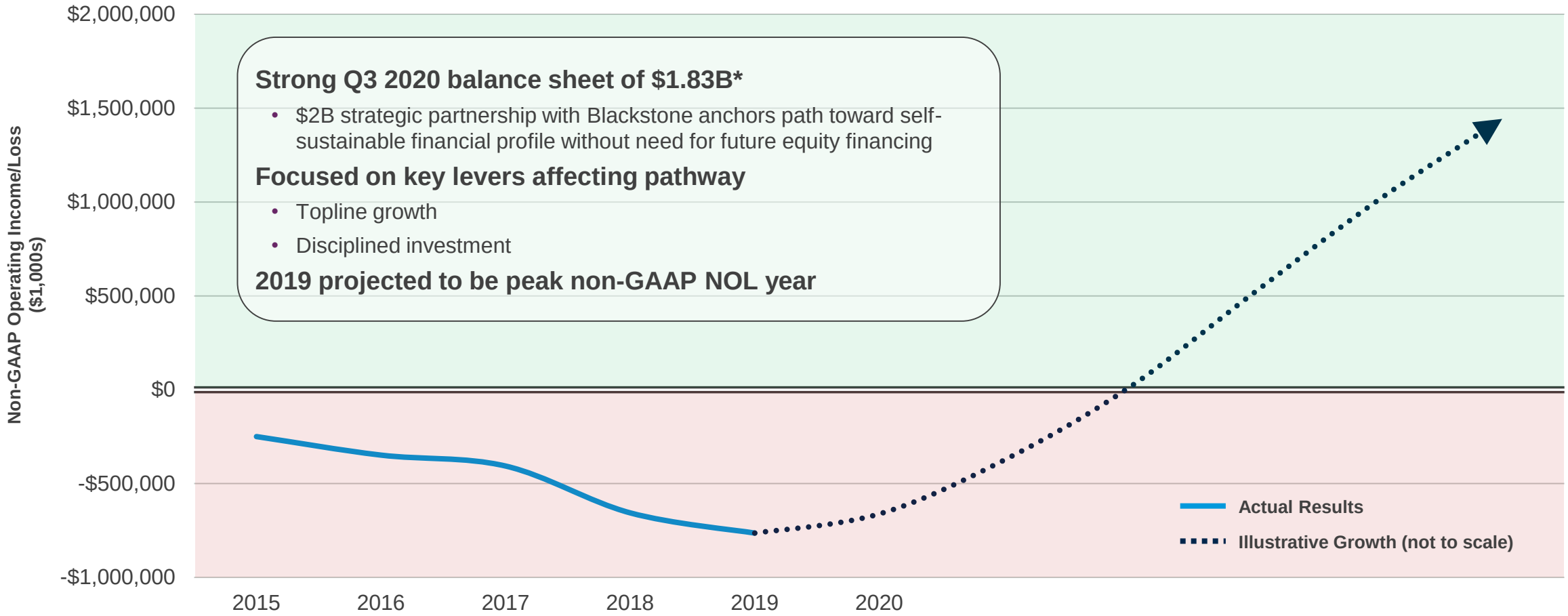
- Expect 2-4 INDs per year
- Large number of opportunities
- Organic capability & growth



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

6. Transition to Self-sustainable Financial Profile

Alnylam Entering Period of Projected Growth



Strong Q3 2020 balance sheet of $1.83B*

- $2B strategic partnership with Blackstone anchors path toward self-sustainable financial profile without need for future equity financing

Focused on key levers affecting pathway

- Topline growth
- Disciplined investment

2019 projected to be peak non-GAAP NOL year

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

* Including cash, cash equivalents, marketable securities

Building a Top-Five Biotech

Potential for Significant Transformation of Alnylam over Next 5 Years

2020

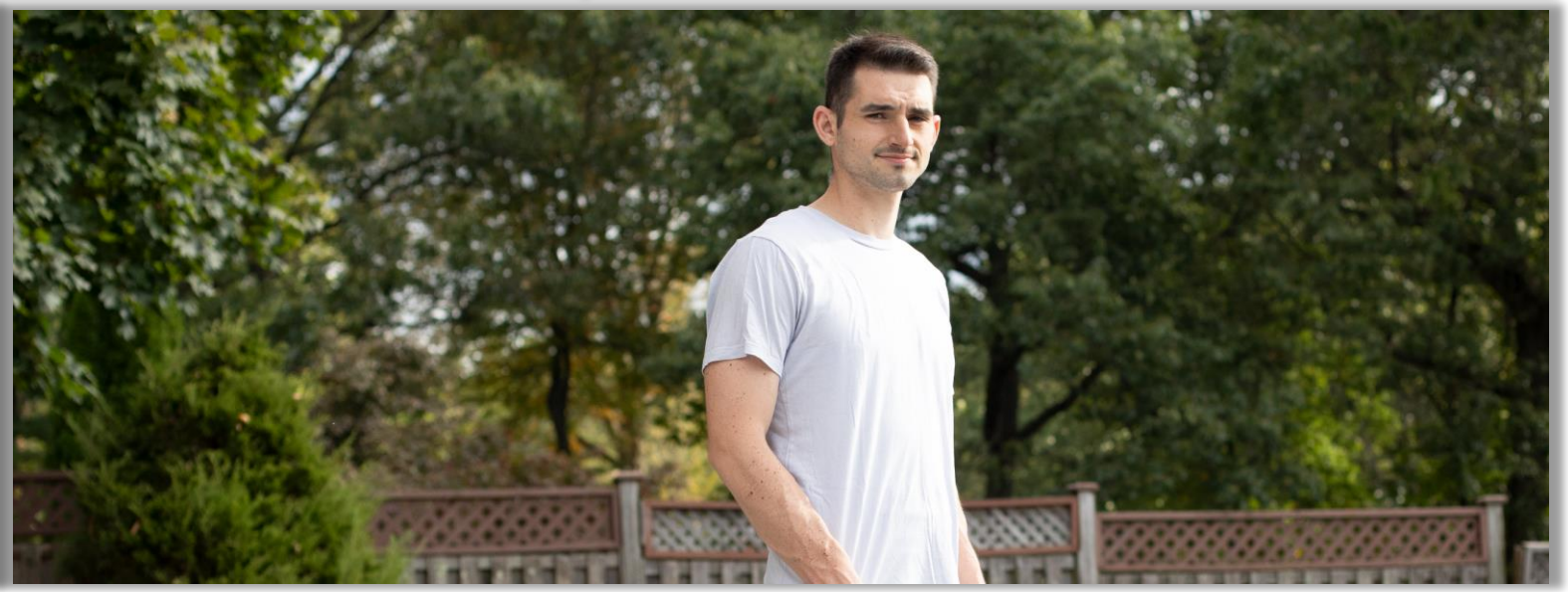
Rare Diseases	
4	Approved Products
Initial Indications	
6	Late Stage Programs
4	STArs
~20 Markets	
~1K	Employees
CMOs	

2025

Prevalent Diseases	
6+	Approved Products
Multiple Indications	
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

Patients, Our Core Focus!



VOICES OF **PATIENTS & CAREGIVERS**

“I'm so much more than this disease, and I can put it in its place and do the things that I love to do with the people who I most love and adore in my life.”

Amy, treated with ONPATTRO®

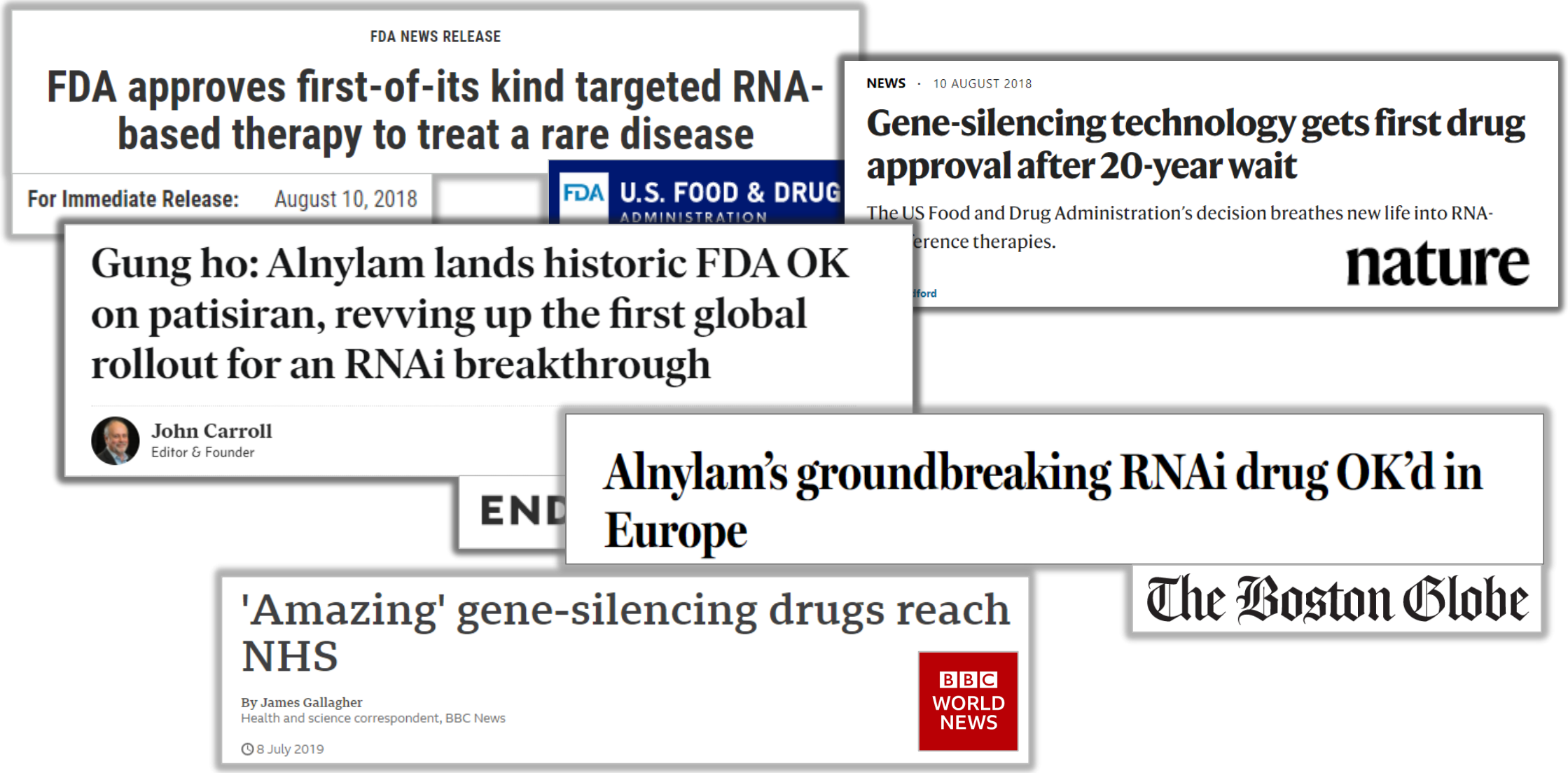
Alnylam® PHARMACEUTICALS

Bringing RNAi Therapeutics to Patients Around the World

Yvonne Greenstreet, MBChB, MBA
President, Chief Operating Officer

Alnylam PHARMACEUTICALS

Advent of Commercial RNAi Therapeutics



Cece
Living with hATTR Amyloidosis

ATTR Amyloidosis

Rare, Progressively Debilitating, and Often Fatal Disease

Description

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

Hereditary ATTR (hATTR) Amyloidosis

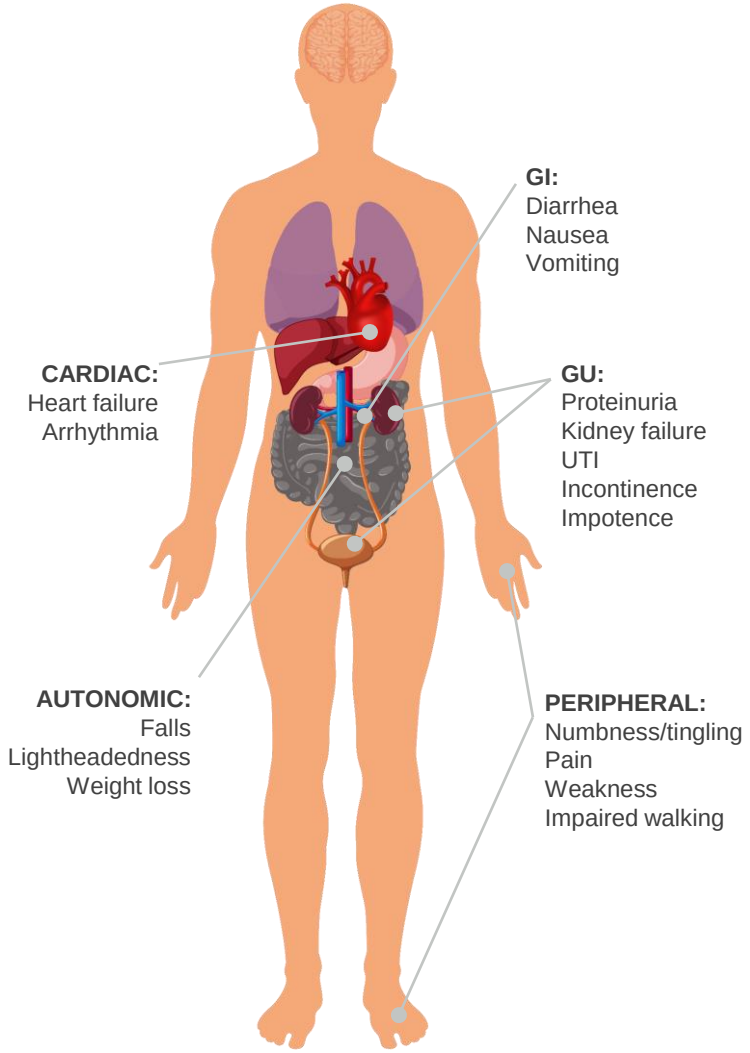
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

patients worldwide



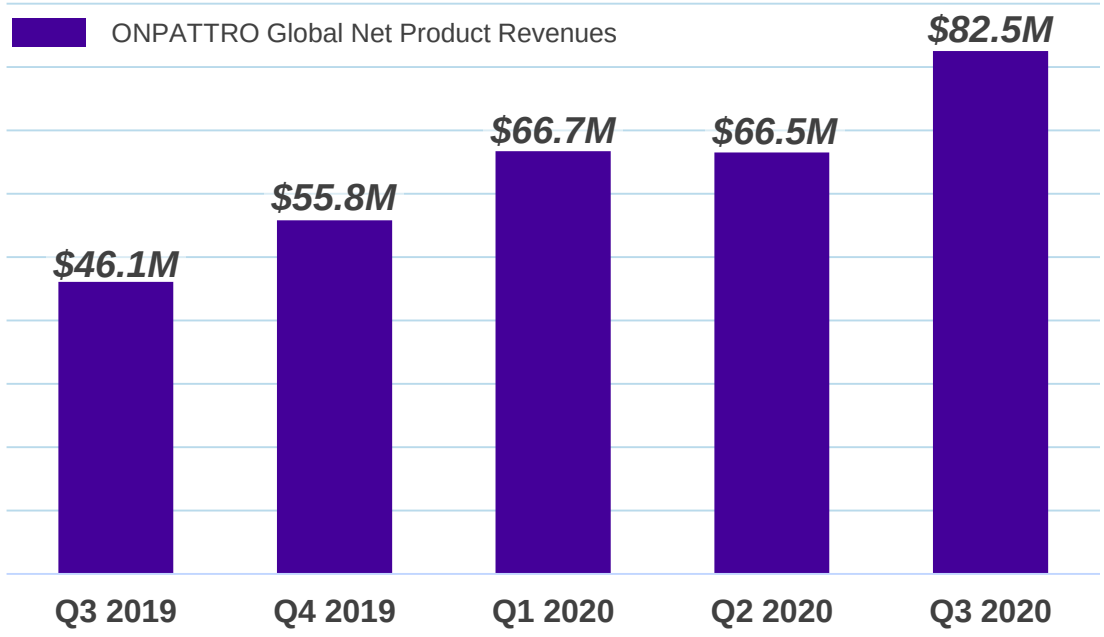
[1] Coelho T, et al. N Engl J Med. 2013;369(9):819-829
* Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012

ONPATTRO® Launch Update: Q3 2020

Strong Performance with Steady Growth in Patients Worldwide on Commercial ONPATTRO

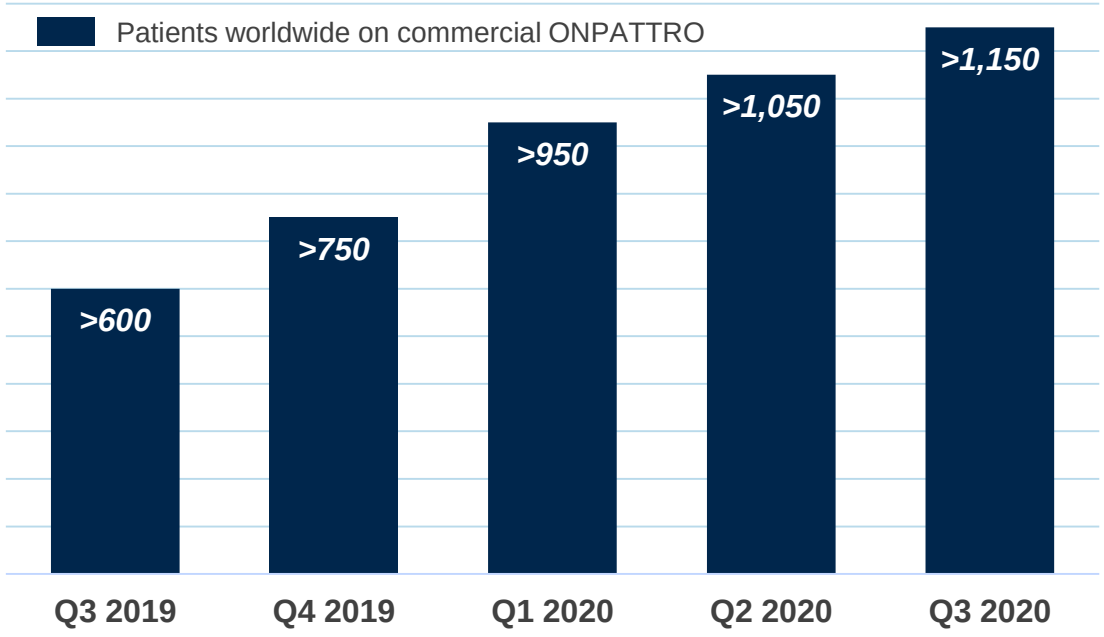
$82.5M

ONPATTRO Global Q3
Net Product Revenues



>1,150

Patients Worldwide on Commercial
ONPATTRO at end of Q3 2020



Yeliz
Living with Porphyria

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

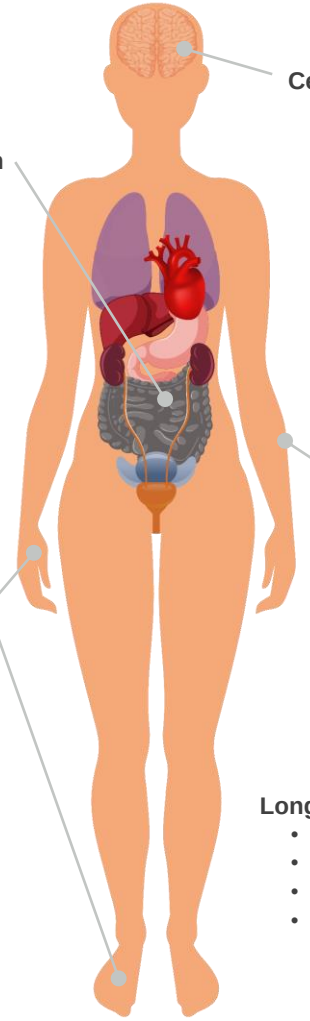
female

commonly misdiagnosed

Patient Population

~3,000

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



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

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

Cutaneous†
- Lesions on sun-exposed skin

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

Long-term Complications
- Liver disease
- Chronic kidney disease
- Hypertension
- Neuropathy

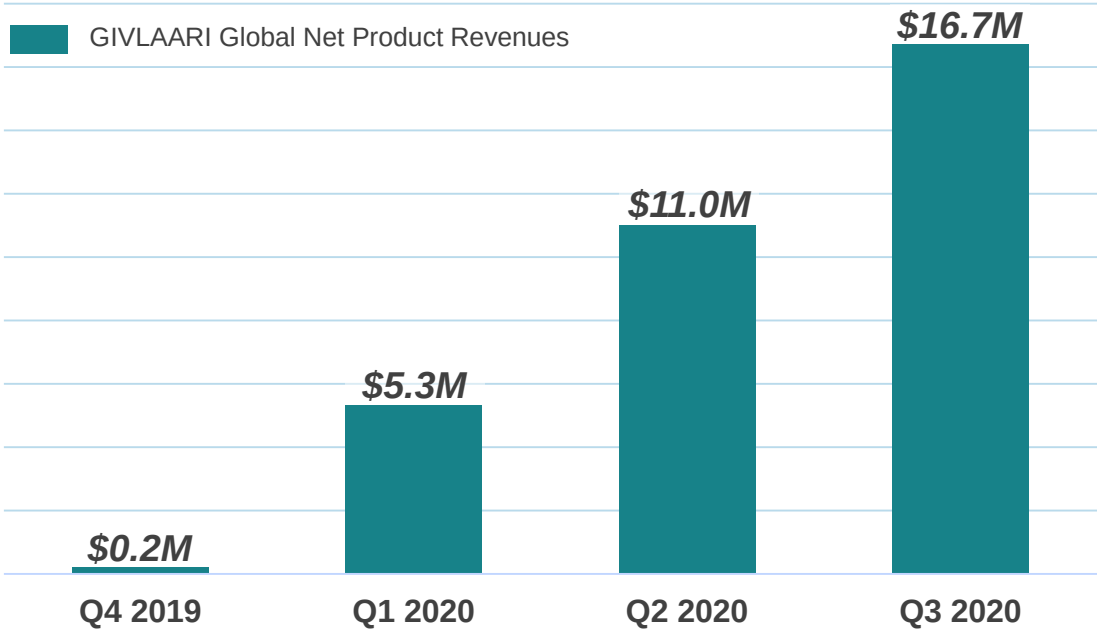
[1] Elder et al. J Inherit Metab Dis 2013;36:849–57; 2. Data on file, IBM MarketScan Commercial Claims and Medicare Supplemental Database
† Symptoms specific to hereditary coproprophyria and variegate porphyria

GIVLAARI® Launch Update: Q3 2020

Strong Initial Demand

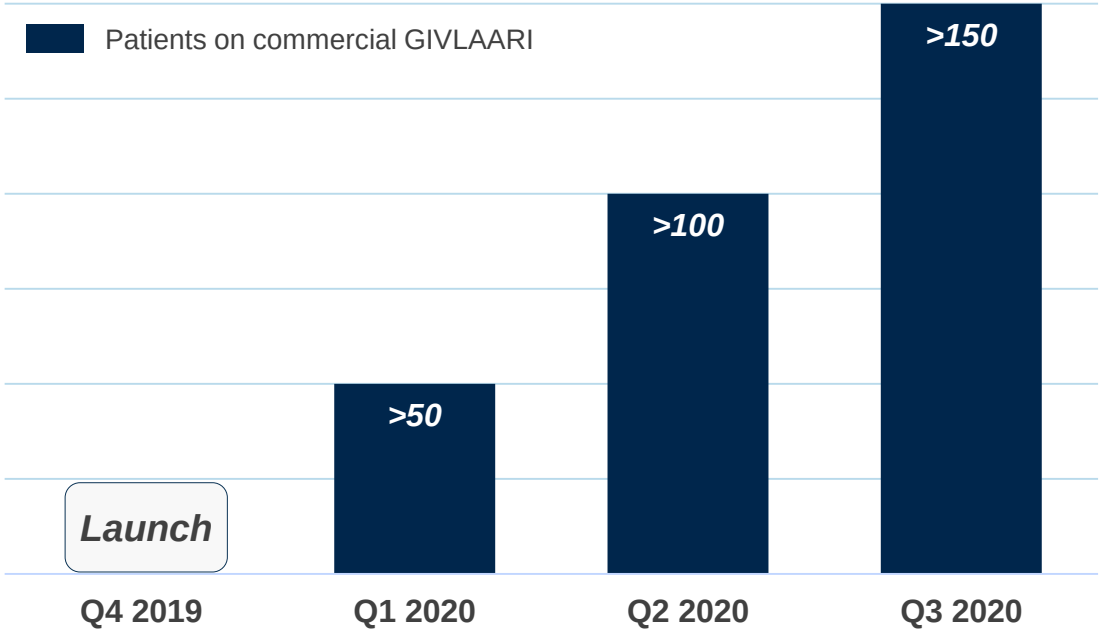
$16.7M

GIVLAARI Q3
Global Net Product Revenues



>150

Patients on Commercial GIVLAARI
at end of Q3 2020



Benson
Living with Primary Hyperoxaluria Type 1

Primary Hyperoxaluria Type 1

Ultra-Rare Orphan Pediatric Disease with Significant Disease Burden

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

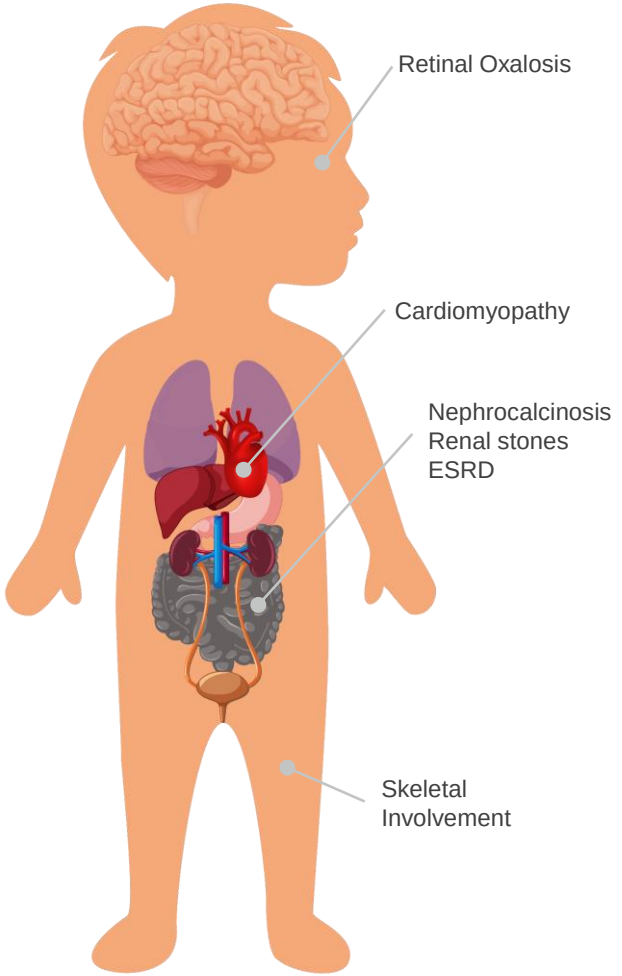
pediatric

very limited treatment options

Patient Population

~3,000

potentially symptomatic in U.S./EU[1]

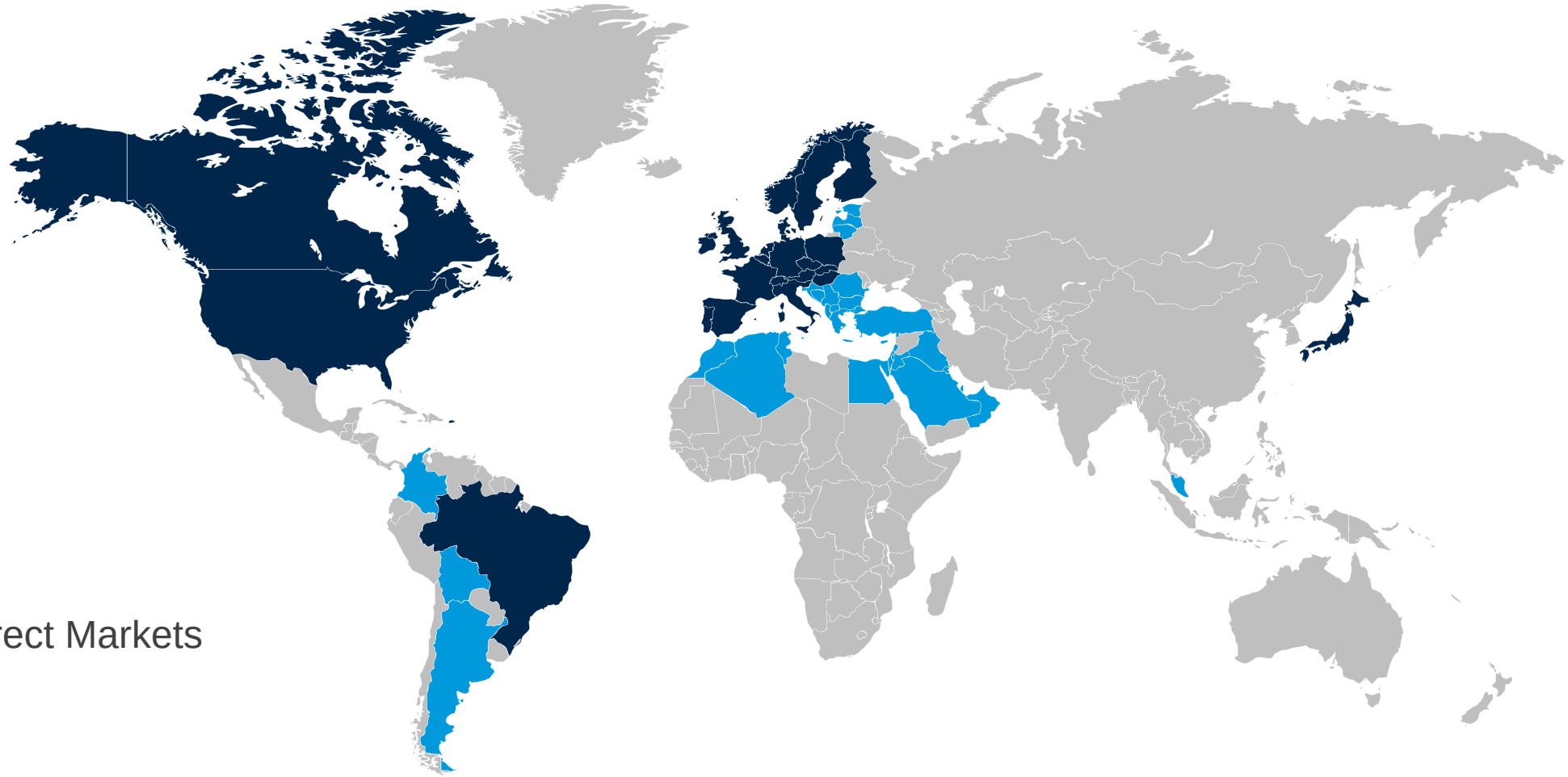


[1] Includes patients that are presymptomatic, subclinical, or symptomatic

The third RNAi therapeutic is

NOW APPROVED IN THE EU & U.S.

Alnylam Global Commercial Footprint

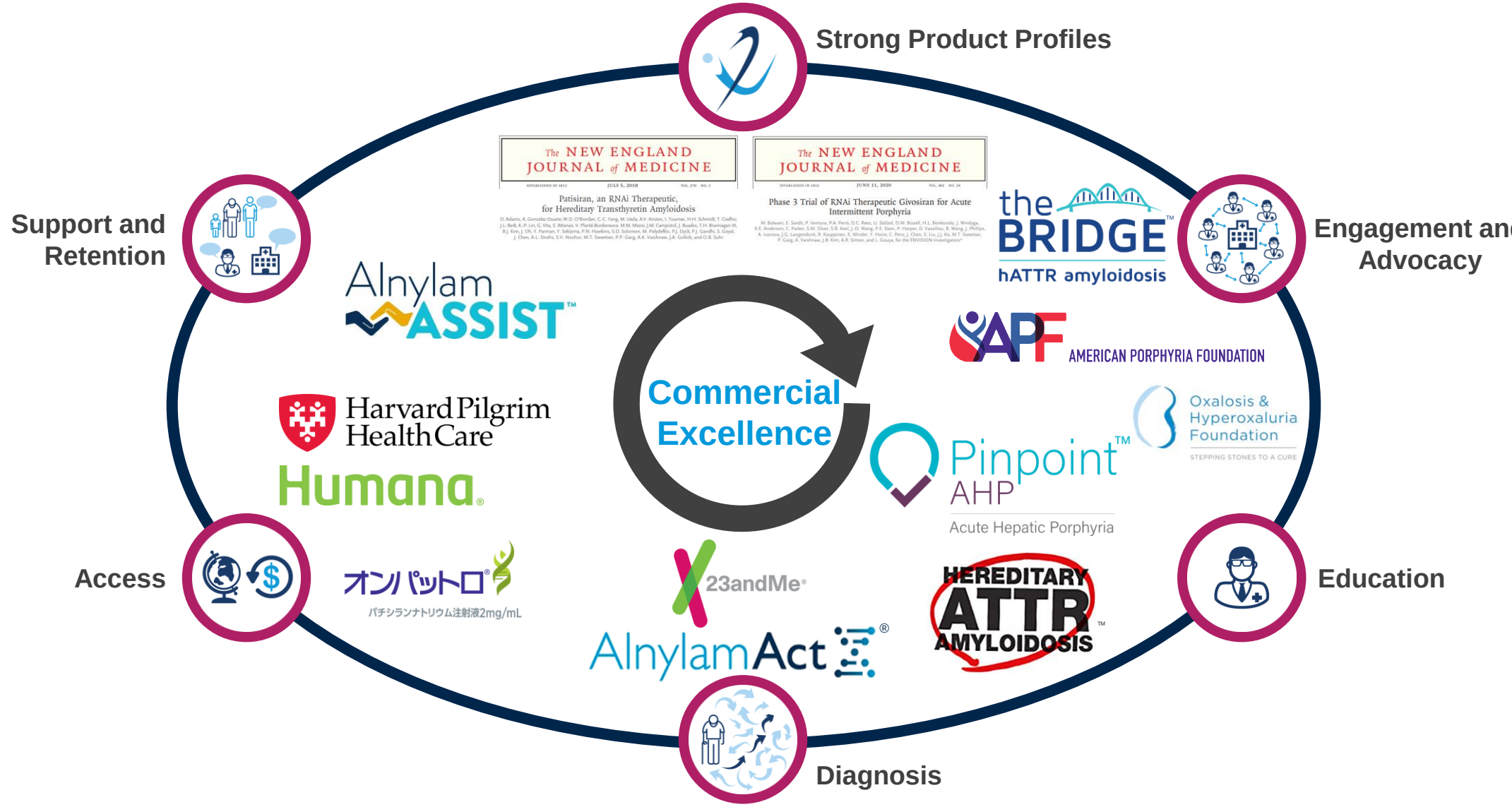


24 Direct Markets

34 Distributor Markets

Bringing RNAi Therapeutics to Patients Worldwide

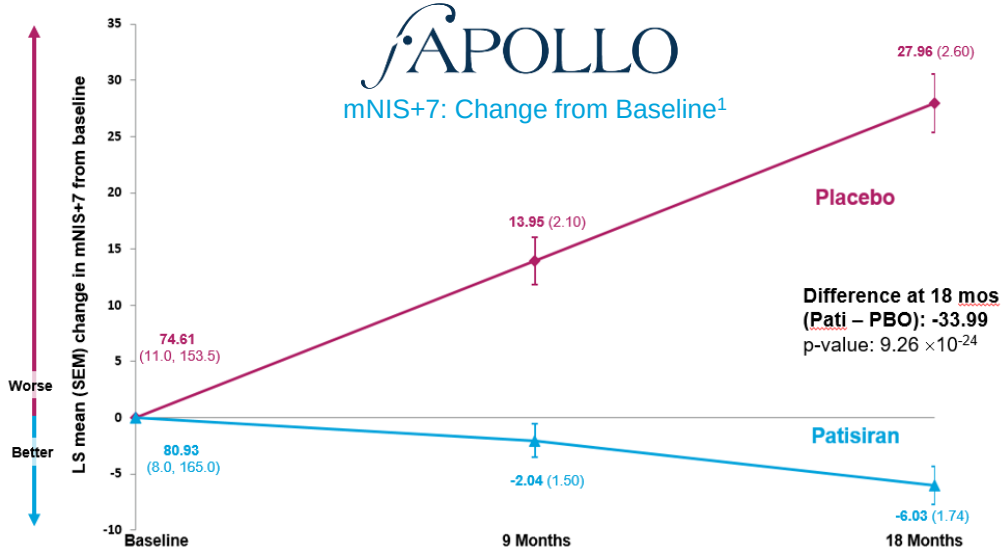
Robust Medical Affairs and Commercial Platform Leverageable for Continued Success



RNAi Therapeutics – Phase 3 Study Results

APOLLO

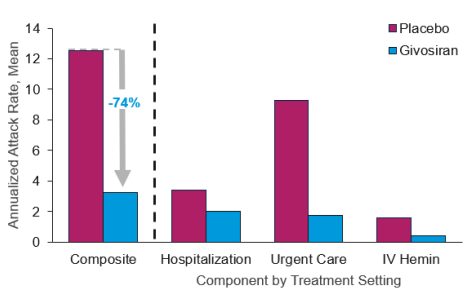
mNIS+7: Change from Baseline[1]



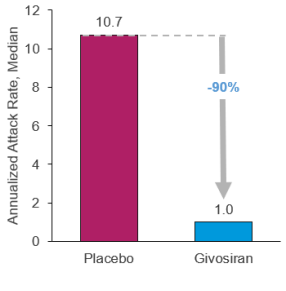
ENVISION

Primary Endpoint	Givosiran (N=46)	Placebo (N=43)	Rate Ratio (95% CI) (givosiran vs placebo)	P-Value
Composite Annualized Attack Rate, Mean	3.2 (2.25, 4.59)	12.5 (9.35, 16.76)	0.26 (0.16, 0.41)	6.04 x 10^{-9}

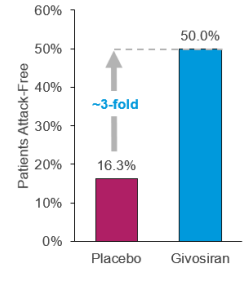
Composite and all endpoint components reduced



Reduction in median composite attack rate

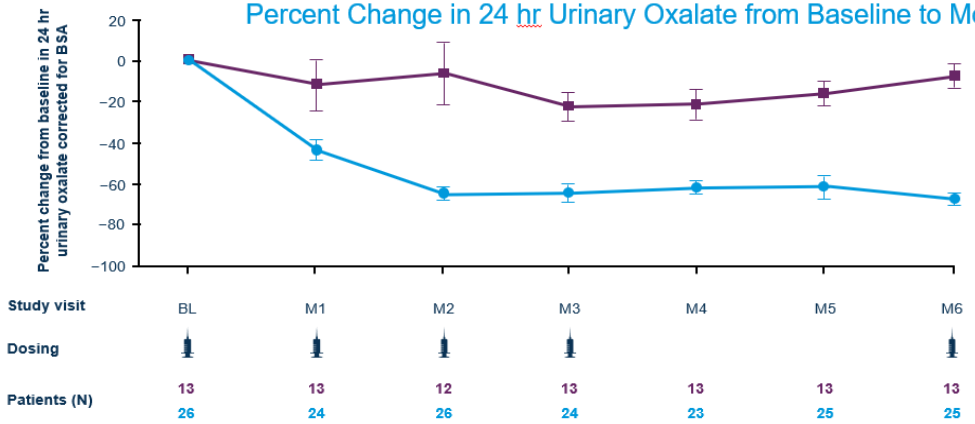


Increase in patients attack-free



ILLUMINATE•A

Percent Change in 24 hr Urinary Oxalate from Baseline to Month 6



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

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

Mean maximal reduction: 76.0%

Pati, patisiran; PBO, placebo; CFB, change from baseline
mNIS+7 reference range: 0-304 points
Data in ILLUMIANTE-A graph are mean ± SEM of observed values; The Month 6 dose defines the beginning of the 54-month extension period
BL, baseline; BSA, body surface area; hr, hour; LS, least squares; M, month; SEM, standard error of the mean

Patient Centric Approach

Ongoing Patient Engagement Integral to Excellence in Rare Diseases

Building cooperative partnerships globally to serve patient communities across a range of disease areas

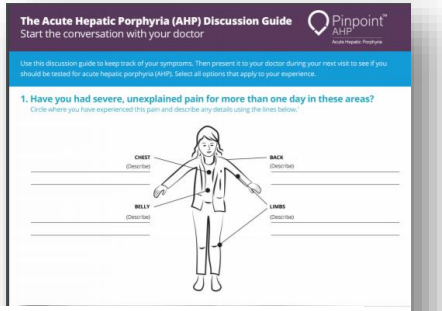
- Engagement with advocacy groups provides important avenue for educating patients, caregivers, and healthcare providers
- Integration of patient voice throughout drug development process creates collaborative effort with common goal
- Disease education empowers patients to make informed decisions about their health and share learnings within their communities

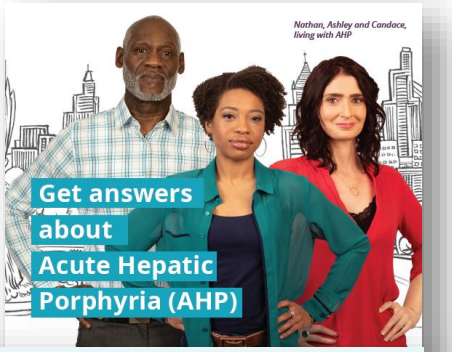
Amyloidosis Research Consortium

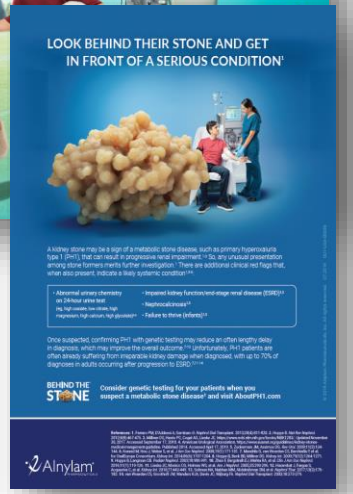
APF AMERICAN PORPHYRIA FOUNDATION

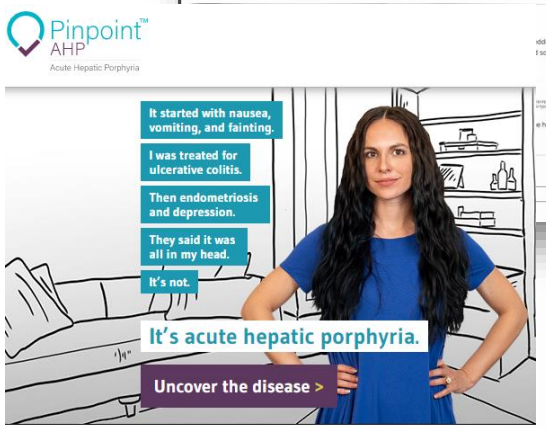
OXAIL EUROPE
European Hyperoxaluria Consortium

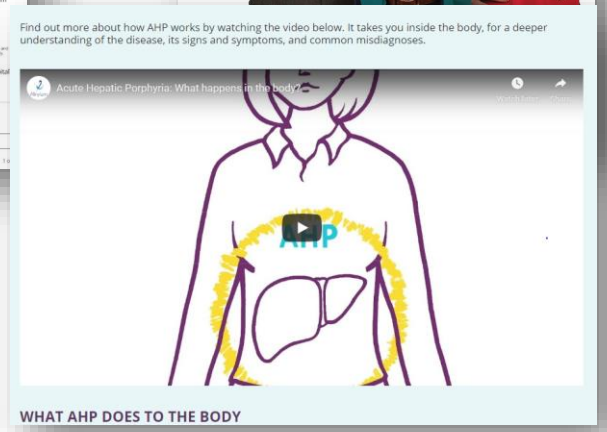
Multiple Disease Awareness Initiatives Ongoing











COULD IT BE ACUTE HEPATIC PORPHYRIA (AHP)?

Education

Genetic Testing and Diagnostic Efforts

Increasing Awareness with Alnylam Act® and Direct-to-Consumer Tests

Alnylam Act®

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., Canada and Brazil* (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

TTR Samples Submitted to Date[1]	**30,612**	**AHP Samples Submitted to Date[1]**	**1,130**
Positive TTR Samples Submitted to Date[1]	**1,796**	**Positive AHP Samples Submitted to Date[1]**	**104**

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

23andMe®

23andMe offers direct-to-consumer genetic testing that provides consumers with information about health, ancestry, traits and more, including whether they carry genetic markers for diseases such as hATTR amyloidosis

Through a joint branded campaign (“+myFamily”), Alnylam offers free 23andMe tests to 1st degree relatives of eligible identified TTR mutation carriers in the U.S.

- This program went live in July 2019
- >1,160 kits already supplied through program[2]

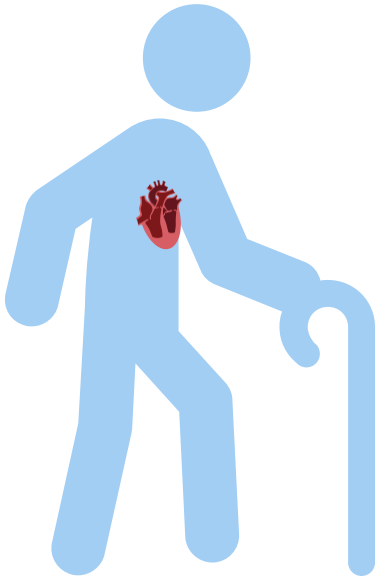
*Alnylam Act only available for hATTR amyloidosis genetic testing in Brazil.

[1] As of 28October2020; includes hATTR Amyloidosis, Acute Hepatic Porphyria, and Primary Hyperoxaluria Type I. [2]As of September 2020

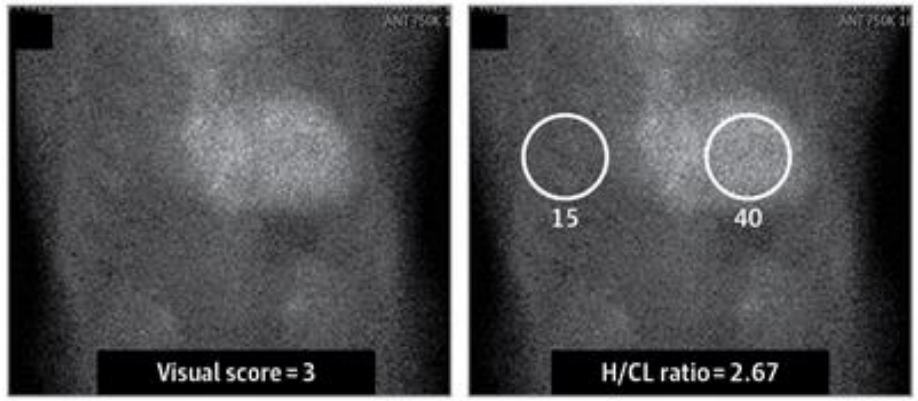
At no time does Alnylam receive patient-identifiable information. Alnylam receives contact information for healthcare professionals who use the Alnylam Act program

Identifying Signs and Symptoms Crucial for Expediting Diagnosis

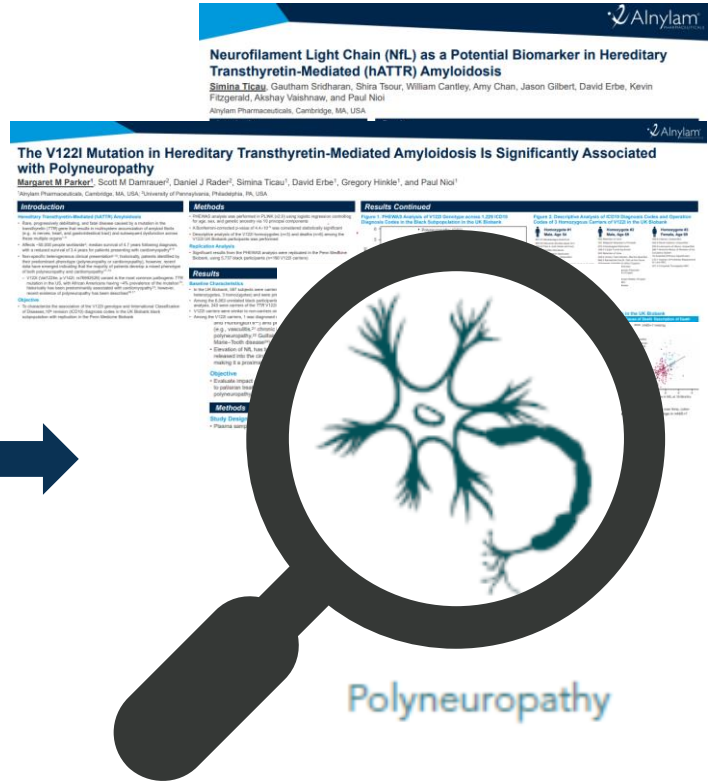
Improving Diagnosis through Evidence Generation



^{99M}Tc-PYP Scan of Patient with ATTR Cardiac Amyloidosis[1]



Increasing use of PYP scans to diagnose hATTR amyloidosis



>50%

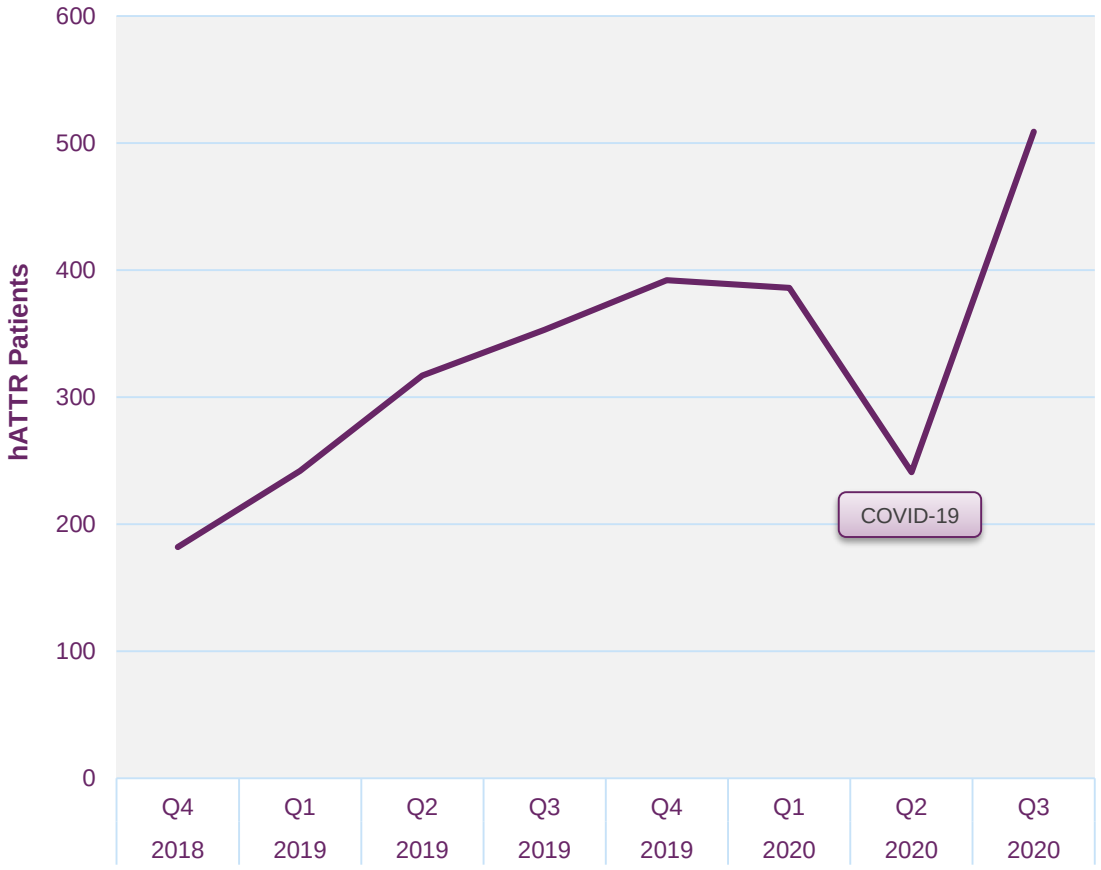
of hATTR amyloidosis patients with confirmed cardiomyopathy found to have polyneuropathy symptoms

[1]Castano A. et al. *JAMA Cardiol.* 2016;1(8):880-889. doi:10.1001/jamacardio.2016.2839

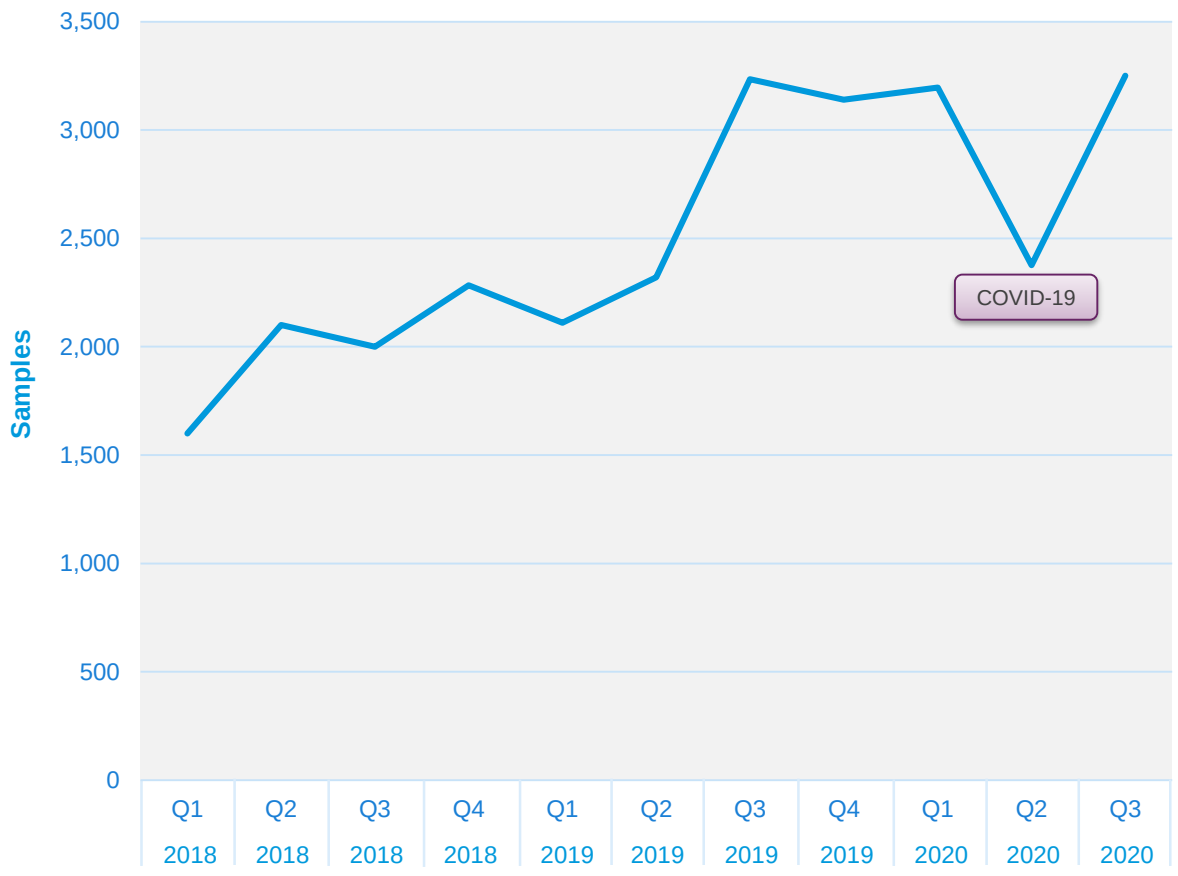
Ongoing Growth in Diagnostic Efforts

Evidence of Expanding Disease Awareness

Quarterly PYP Scan Volume



Quarterly TTR Samples Submitted to Alnylam Act



Data Source: Biweekly hATTR Pulse Claims data

1. hATTR patients: Pulse data is a subset of Komodo's Claims data. It is focused on hATTR Commercial patients
2. PYP volume is subject to change due to lag in Claims data. : ~ 50% of medical claims data is captured within 2.5 weeks, 80% within 6 weeks; ~ 50% of pharmacy claims data is captured within 1.5 weeks, 87% within 2 weeks. Minor changes are also observed in data older than 6 weeks due to COVID related billing lag from HCOs.

Industry Leading, Value-Based Philosophy

Leveraging Innovation to Help Patients and Deliver Value

~30

Signed Value-Based Agreements (VBA) with U.S. payers in aggregate for ONPATTRO and GIVLAARI

>98%

of U.S. lives with confirmed access to ONPATTRO across commercial, Medicare, Medicaid and other government payer categories

>93%

of U.S. lives with confirmed access to GIVLAARI across commercial, Medicare, Medicaid and other government payer categories

75%

of commercially insured U.S. patients have zero copay for ONPATTRO[1]

87%

of commercially insured U.S. patients have zero copay for GIVLAARI[1]

0

Price increases for Alnylam products

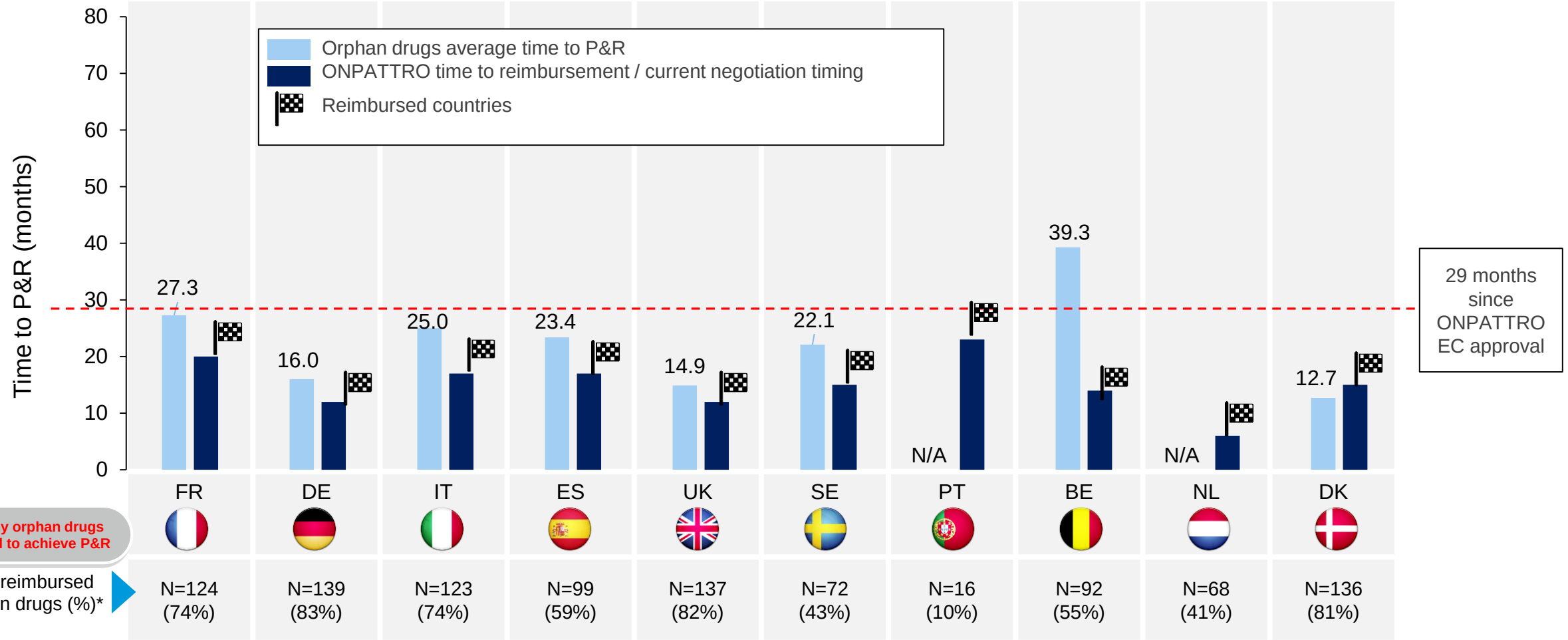
Data as of November 2020

[1] Includes patients utilizing commercial co-pay, Managed Medicare and Medicare FFS plus supplement

For more information, visit https://news.alnylam.com

ONPATTRO Achieved Reimbursement in Major EU Countries Faster Than Average of All EMA Approved and Reimbursed Orphan Drugs

In some countries only few orphan drugs achieved reimbursement at all



Source: PriceCentric for analogue data. *Number of drugs included in the P&R DB, divided by number of approved EMA orphan drugs (n=167).

Please note that the % should be considered only as a proxy of approval rate. Reasons of uncertainty: i) certain products could be approved but not listed in the national DB; ii) certain products are listed in the national DB, but they are not reimbursed. PT, NL time to P&R not available. From literature average time to P&R: PT=27.5m, NL=24.2m.

Access

ONPATTRO … aster Than Average of A…

Source: PriceCentric for analogue …

Please note that the % should be c…

ii) certain products are listed in the …

THE WALL STREET JOURNAL. WSJ

Drugmakers Test New Ways to Pay for Six-Figure Treatments

Public pressure, insurer pushback and better data are driving drug companies to tinker with how they get paid

… In November, Alnylam said it would calibrate the $575,000-a-year price of newly approved Givlaari, depending on how patients respond to the drug and how many take it. Givlaari treats acute hepatic porphyria, an inherited liver condition in an estimated 3,000 patients in the U.S. and Europe that often requires hospitalization.

Alnylam CEO John Maraganore said health plans that have signed on to a value-based contract might pay full price for a drug only if a patient showed benefits like those from the clinical trial.

PHOTO: RYAN EMBERLEY/GETTY IMAGES FOR KLICK INC.

Public and private health insurers that agree to participate in the program will pay full value only if patients show a benefit similar to clinical trials, Alnylam Chief Executive John Maraganore said. The company also will charge less if more patients than expected take the therapy.

The concessions could help Alnylam secure reimbursement from health plans that otherwise might recoil at such a high price tag, while maximizing prescriptions, Dr. Maraganore said. "We can work together without creating misaligned incentives around the cost of a new medicine," he said…

Access

Ongoing Support from Alnylam Assist®

Comprehensive Program Dedicated to Helping Guide U.S. Patients Through Treatment

- **Dedicated Case Manager**
- **Benefit Verification**
- **Financial Assistance for Patients**
- **Treatment Coverage Explanation**
- **Coding and Billing Aid**
- **Disease and Product Education**
- **Ordering Assistance**

Patient Support Program Leverageable Across Therapeutic Areas of Operation

- Alnylam Assist will connect patients with dedicated Alnylam Case Manager who can provide personalized support throughout treatment process
  - Case Managers can help patients determine coverage requirements and explain requirements and processes for prior authorizations, claims, and appeals
- Eligible patients may qualify for Alnylam Assist Quick Start Program, Patient Assistance Program (PAP), or Commercial Copay Program
- Patient Education Liaisons are available to help patients gain better understanding of their disease

Alnylam ASSIST™

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

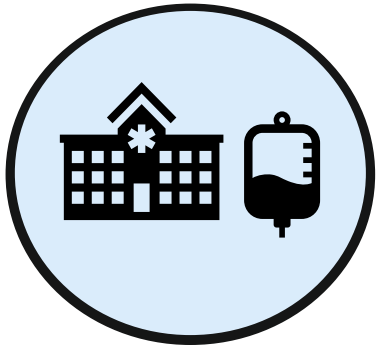
Commercial Adaptability

Patient Support and Virtualization during Pandemic

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

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

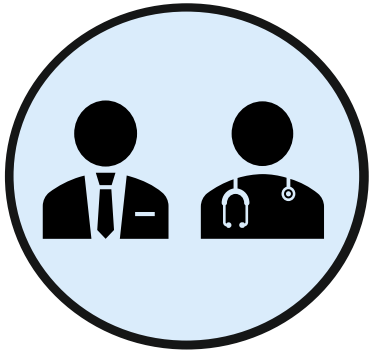
OXLUMO™ (lumasiran) for injection 94.5 mg/0.5 mL



Working on global scale to help new and existing patients receive drug at appropriate sites of care, including at home

ONPATTRO Home Infusion %

December 2019	November 2020
US Commercial – 9%	*US Commercial – 20%*
CEMEA – 17%	*CEMEA – 36%*



Customer-facing field teams leveraging virtual and digital platforms to maintain active engagement with healthcare providers, payers, and patients

Ongoing commercial excellence underpinned by effective adaptability

Robust Commercial Platform Supports Expansion to Large Indications

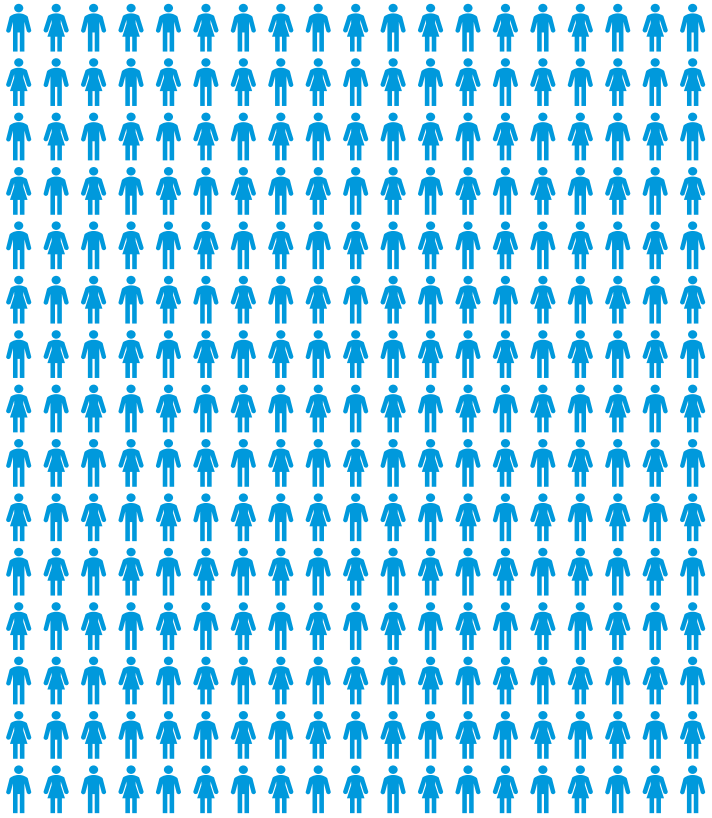
RARE

ONPATTRO-PN
GIVLAARI
OXLUMO
Vutrisiran-PN

Fitusiran
ALN-AAT02
ALN-APP
ALN-HTT

SPECIALTY

ONPATTRO-CM
Vutrisiran-CM
Cemdisiran

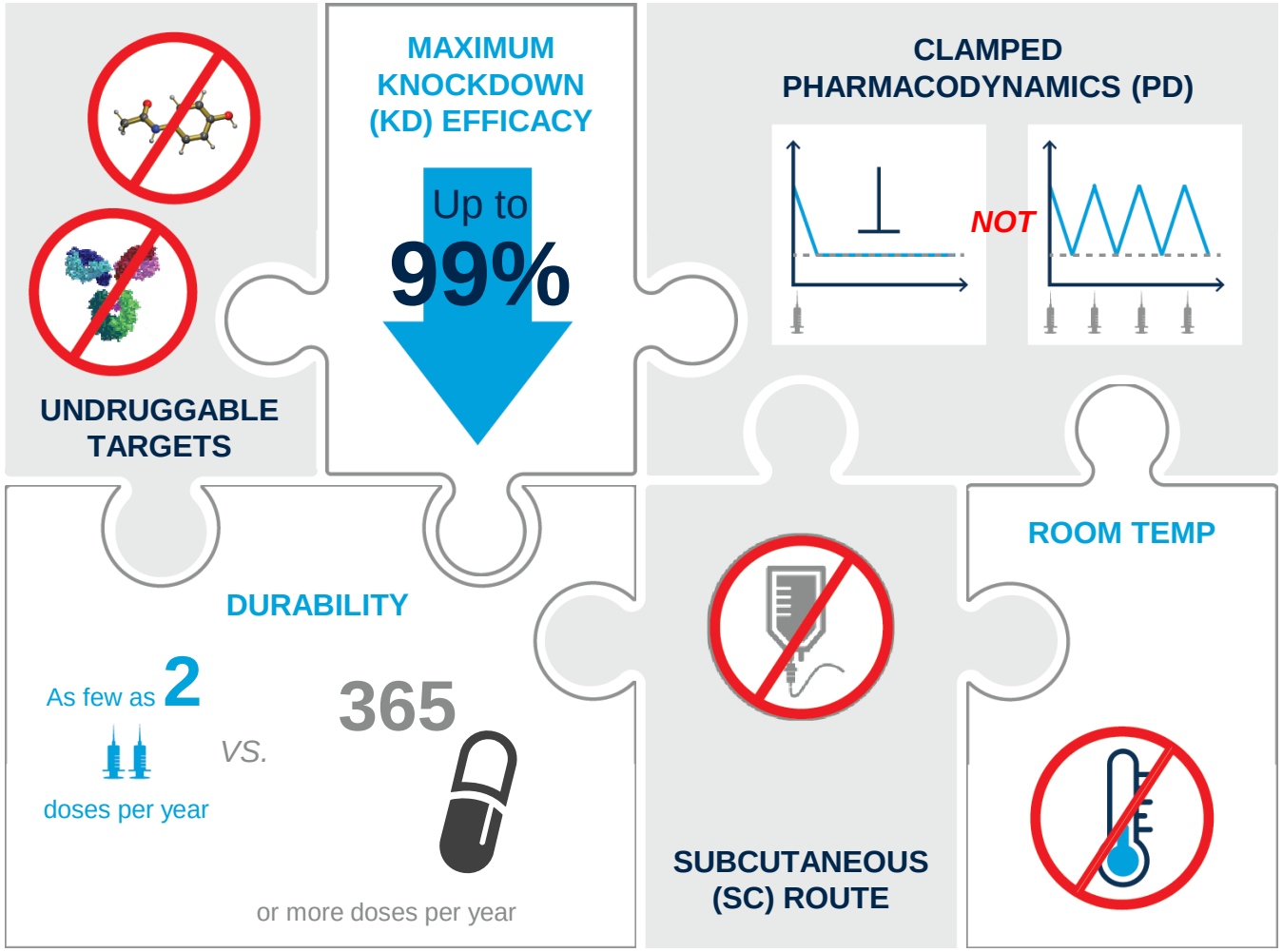


PREVALENT

Leqvio® (inclisiran)
ALN-HBV02 (VIR-2218)
ALN-AGT
ALN-HSD

Key Features of Alnylam RNAi Therapeutics

Platform Profile Well-Suited for Large Indications



Alnylam RNAi Platform

- Infrequent, subcutaneous administration creates dosing flexibility for patients and eases treatment burden
  - Potential for quarterly and biannual dosing
- Wide therapeutic index with potential for transformative outcomes
- Extensive human safety experience across multiple indications, including large market indications such as hypercholesterolemia

Significant Unmet Needs in ASCVD Treatment Despite PCSK9 mAbs

Significant unmet needs in ASCVD

40%	Adults WW have high LDL-C; ASCVD leading cause of death WW
50m+	Patients across key markets with ASCVD or FH on current SOC not at goal
7%	Treated patients statin intolerant[1]
60%+	Patients treated with statins +/- ezetimibe do not meet goal[2]

Shortcomings of current PCSK9 mAbs treatments

Expensive	Prices at launch above cost-effective benchmarks[3]
Reimbursement hurdles	Leading to 80% of PCSK9i claims being initially rejected[4]
Affordability hurdles	Leading to 50% abandonment rate for PCSK9i after 90 days[5]
Inconvenient	Up to 26 injections per year[6], and cold chain requirement

Persistent and underserved market in ASCVD → Inclisiran could help tackle current issues with existing treatments

Source: DRG (2019), Novartis Commercial team. 1. A Comparison of 2 Claims-Based Algorithms by Bellows et al. JMCP September 2017 Vol. 23, No. 9. 2. Boekholdt et al. Very Low LDL-C levels and CVD Risk JACC VOL 64.No 5 2014:485-94. 3. FonarowGC, KeechAC, Pedersen TR, et al. Cost-effectiveness of Evolocumab Therapy for Reducing Cardiovascular Events in Patients With Atherosclerotic Cardiovascular Disease (2017). 4. NavarAM, Taylor BT, FlevitzE, et al. Early challenges for PCSK9 inhibitor prescriptions and patients: rejections and rates unfilled. Abstract 415-08. 5. Hines DM et al. Poster presented at ACC 2017. 6. PCSK9 prescribing informations

Innovative Commercialization Approaches for Large Market Indications

Opportunity for Broad Access Agreements with RNAi Therapeutics

NHS NOVARTIS

Press release

New heart disease drug to be made available for NHS patients

The government is collaborating with pharmaceutical company Novartis to launch a clinical trial for new cholesterol treatment.

Published 13 January 2020
From: Department of Health and Social Care, Department for International Trade, NHS England, and Office for Life Sciences

- Collaboration to offer cutting-edge new cholesterol treatment to tens of thousands of patients at risk of heart disease in coming years
- In a ground-breaking, in-principle agreement with Novartis, introduction of inclisiran on the NHS following approval has the potential to save up to 30,000 lives over the next 10 years
- Innovative manufacturing research collaboration will position the UK as a world-leading destination to develop cutting-edge treatments

Up to 30,000 lives could be saved over the next decade thanks to a proposed pioneering government collaboration with pharmaceutical company Novartis to tackle heart disease – a leading cause of death in the UK.

The yet to be approved drug inclisiran, a treatment to lower cholesterol, will be studied in UK patients as part of a large-scale NHS clinical trial expected to start later this year. Additionally in a world-first, the drug is expected to be available through a population-level agreement – pioneering a game-changing approach to reducing the risk of heart disease

- World-first, population-level health agreement formed by Novartis with National Health Service (NHS) in U.K.
  - Partnership provides secondary prevention ASCVD patients in U.K. with access to inclisiran upon regulatory approval and National Institute for Health and Care Excellence (NICE) assessment
  - Broad-scale clinical trial will be explored to evaluate use of inclisiran in patients at high risk of having their first cardiac event
  - Agreement also creates manufacturing research collaboration with goal of improving efficiency/scale of therapeutic oligonucleotide manufacturing in U.K.
- NHS agreement demonstrative of innovative access approaches possible with RNAi therapeutics in large market indications

Summary

- Ongoing commercial and medical affairs successes enabled by mature global infrastructure
- Robust commercial platform leverageable for successive product launches
- Profile of RNAi therapeutics and commercial platform supports expansion from rare to large market indications

VOICES OF **PATIENTS & CAREGIVERS**

“Since starting treatment with GIVLAARI in the clinical trial, I haven’t experienced any AIP attacks…My mom says she can see the “old Donna” coming back, and she really missed me.”

Donna, GIVLAARI patient ambassador

Alnylam® PHARMACEUTICALS

Delivering Sustainable Innovation with RNAi Therapeutics

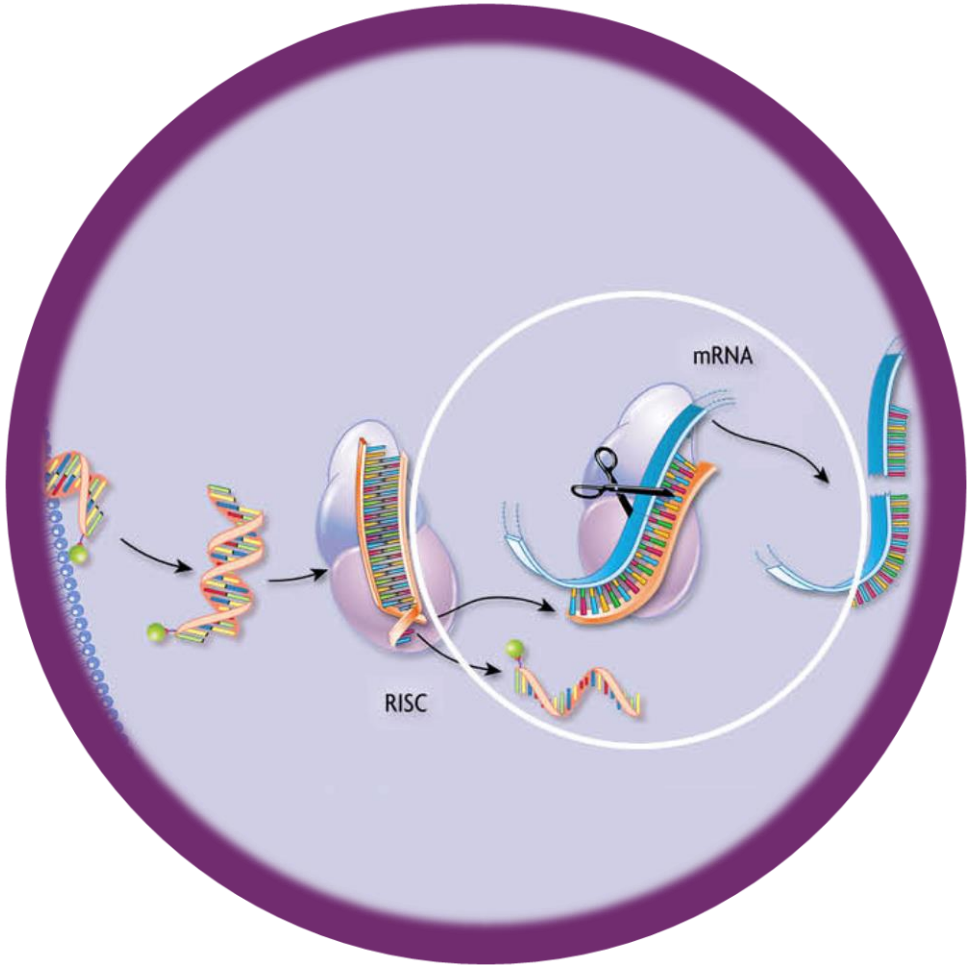
Akshay Vaishnaw, M.D., Ph.D.
President, Research & Development

Alnylam® PHARMACEUTICALS

RNAi Therapeutics: New Class of Innovative Medicines

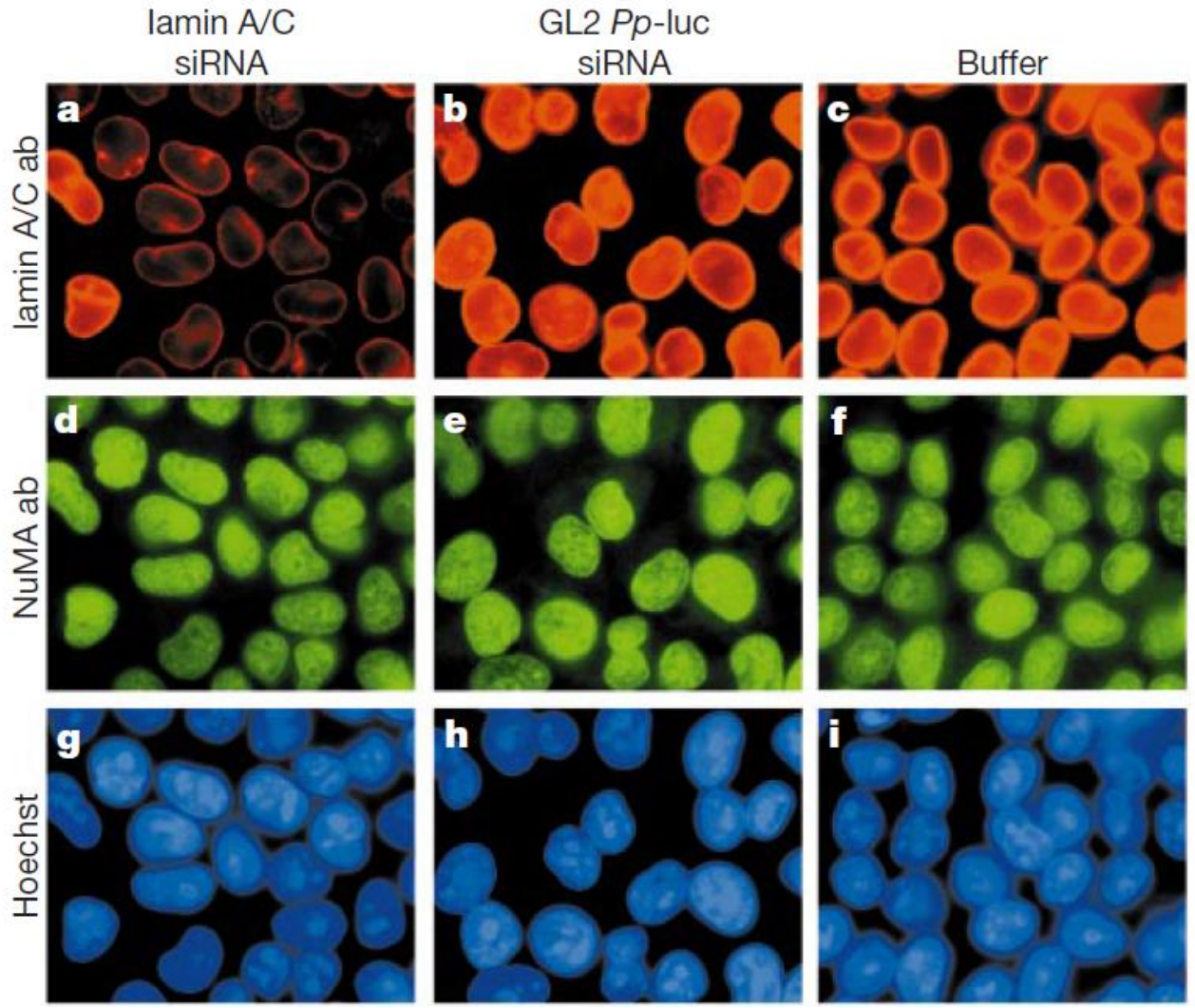
Clinically Proven Approach with Transformational Potential

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



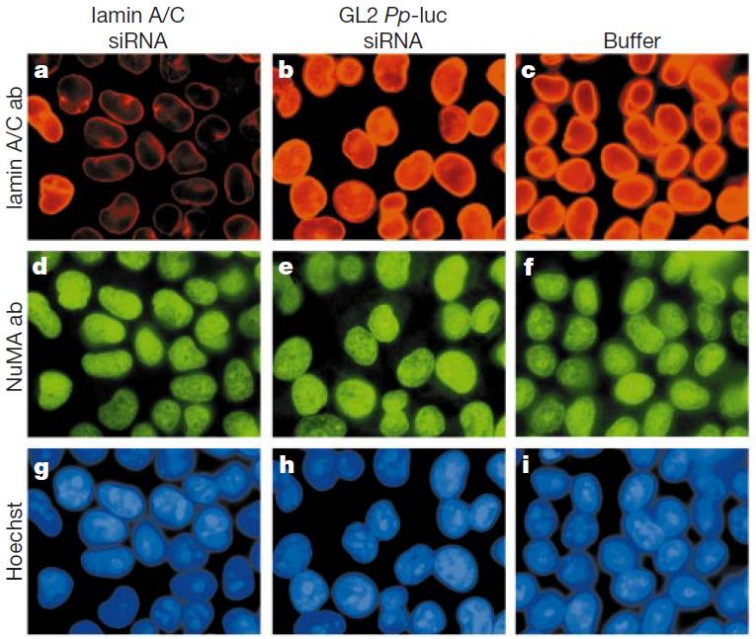
In Vitro Data that Started Alnylam

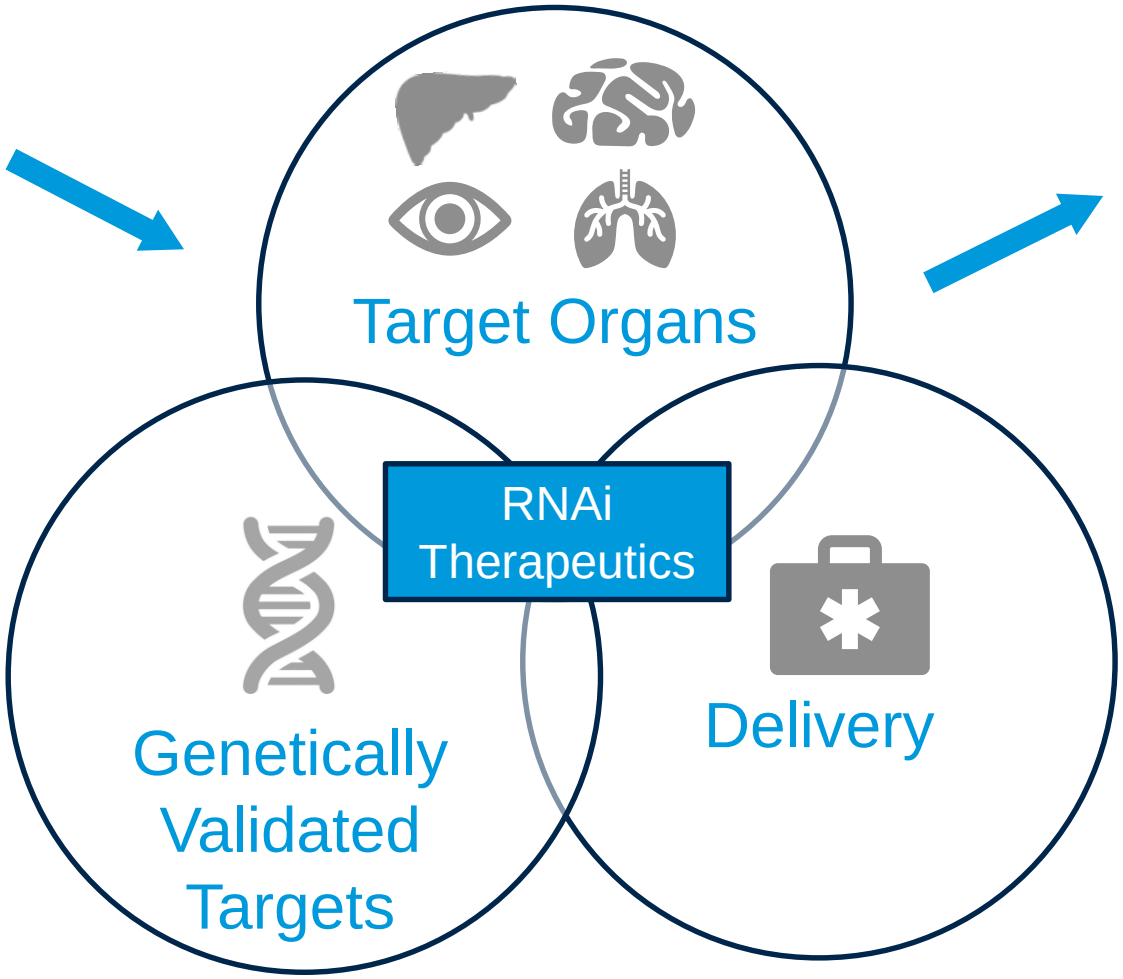
Elbashir et al., Nature, 2001;411:494-98



Focused R&D Strategy

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





Agenda

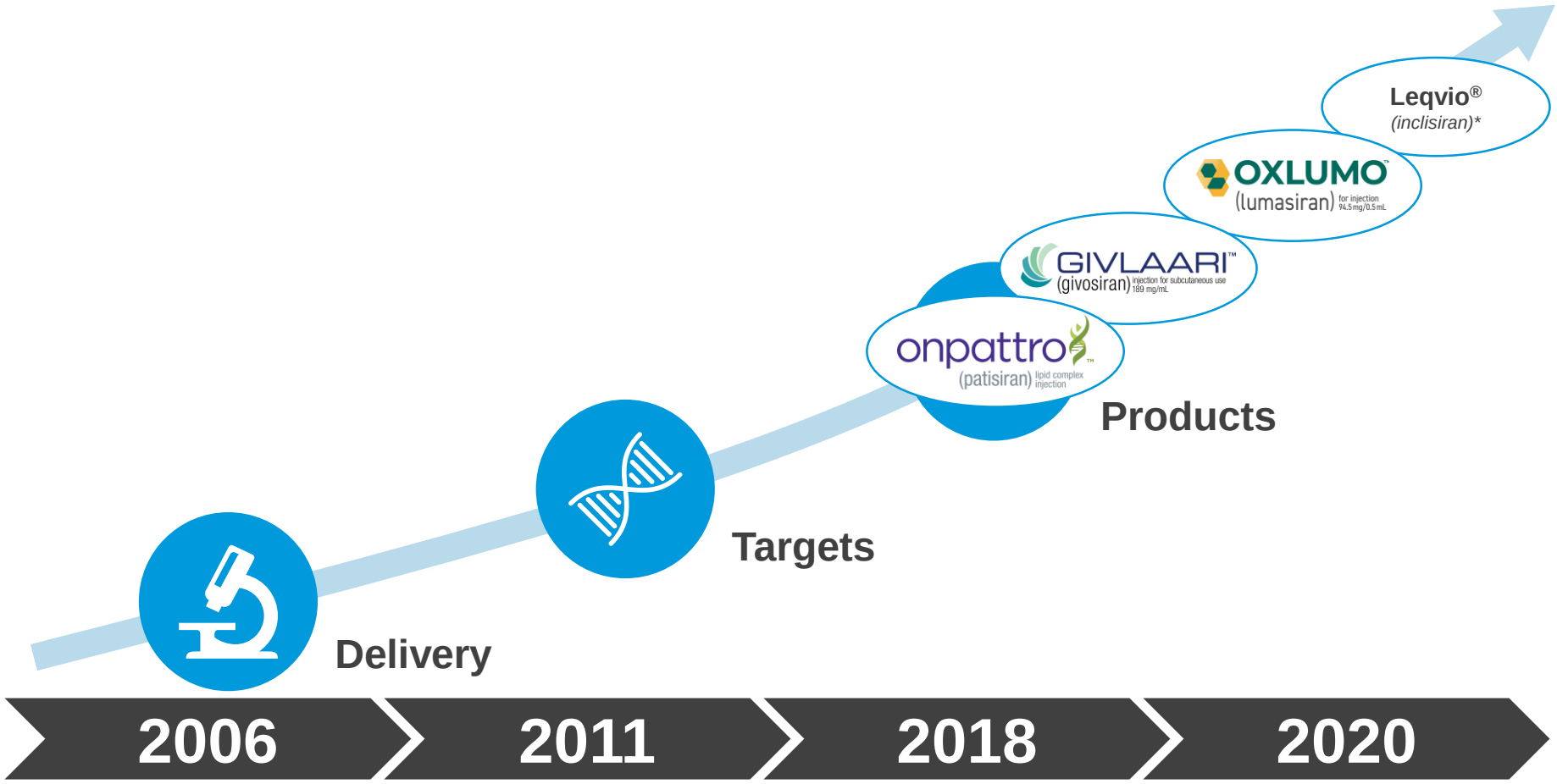
Progress to Date

Evolving the Pipeline

Future Outlook

Alnylam Product Engine

Liver-Focused Pipeline Through 2020



Vutrisiran
Fitusiran
Cemdisiran
ALN-AGT
ALN-HSD
…and more

* Novartis has obtained global rights to develop, manufacture and commercialize inclisiran under a license and collaboration agreement with Alnylam Pharmaceuticals, a leader in RNAi therapeutics
Vutrisiran, fitusiran, cemdisiran, ALN-AGT, and ALN-HSD are investigational RNAi therapeutics. Their respective safety and efficacy have not been evaluated by the U.S. FDA or any other health agency

Alnylam Commercial Products and Late Stage Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

		BREAKTHROUGH DESIGNATION	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION	COMMERCIAL	COMMERCIAL RIGHTS
onpattro (patisiran) lipid complex injection 10 mg/5 mL	*hATTR Amyloidosis*[1]	●			●	Global
GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL	*Acute Hepatic Porphyria*[2]	●			●	Global
OXLUMO™ (lumasiran) for injection 94.5 mg/0.5 mL	*Primary Hyperoxaluria Type 1*[3]	●			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*				●	Milestones & up to 20% Royalties[4] **(Novartis)**
Patisiran	*ATTR Amyloidosis*		●			Global
Lumasiran	*Severe Primary Hyperoxaluria Type 1*		●			Global
Vutrisiran	*ATTR Amyloidosis*		●			Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*		●			15-30% Royalties **(Sanofi)**

[1] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [2] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older; [3] Approved in the U.S. and EU for the treatment of primary hyperoxaluria type 1 in all age groups; [4] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam

As of December 2020

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

Primary Endpoint at 9M^
- Change in mNIS+7 from baseline

Secondary Endpoints at 9M
- Change in Norfolk QOL-DN from baseline
- 10-meter walk test

Secondary Endpoints at 18M Include:
- Change in mNIS+7 from baseline, change in Norfolk QOL-DN from baseline, 10MWT, mBMI, R-ODS

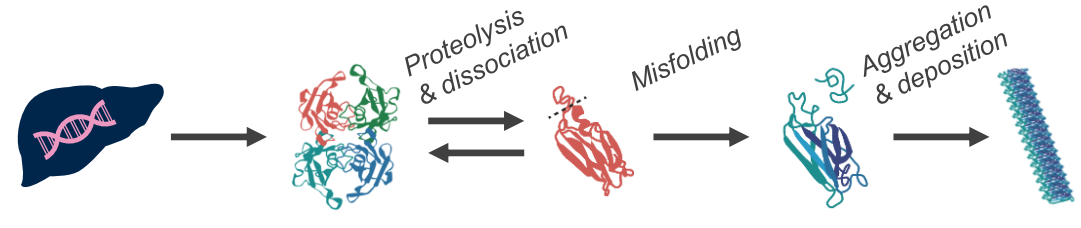
Exploratory Endpoints Include
- NT-proBNP
- Echo parameters
- Technetium (select sites only, change from baseline)

HELIOS-A Phase 3 study **enrollment complete**

Topline results expected **early 2021**

^ Primary endpoint for the study is at 9 months; in the Helios A statistical analysis plan for U.S. submissions, change in Norfolk QOL-DN from baseline will be treated as a co-primary endpoint

Accumulating Evidence for RNAi Therapeutics Across ATTR Amyloidosis



POLYNEUROPATHY

CARDIOMYOPATHY

ONPATTRO
Primary endpoint
- mNIS+7

All secondary endpoints

APOLLO

VUTRISIRAN
Primary endpoint
- mNIS+7

Results expected early 2021

HELIOS-A

PATISIRAN
Post hoc analyses[1]
- Reduction in mortality and hospitalization

Exploratory endpoints
- NT-proBNP, LV thickness, 10-meter walk test

APOLLO

PATISIRAN
IIS[2]
- Clearance of cardiac amyloid, improvement in 6-minute walk test

VUTRISIRAN
Exploratory cardiac endpoints
- NT-proBNP, echo parameters, technetium imaging

Results expected late 2021

HELIOS-A

PATISIRAN
Primary endpoint
- 6-minute walk test

Results expected 2022

APOLLO-B

VUTRISIRAN
Primary endpoint
- Mortality & CV events

Enrolling

HELIOS-B

[1] Solomon S, et al. Circulation 2018

[2] Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI: 10.1016/j.jcmg.2020.07.043

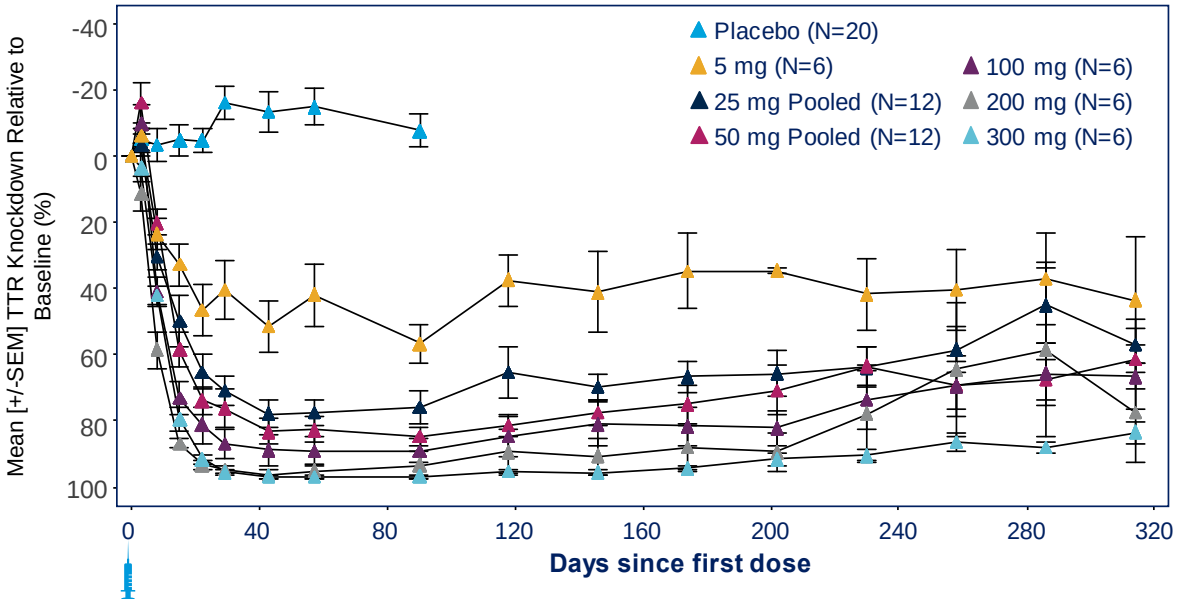
Opportunity for Biannual Vutrisiran Dosing Regimen

Modeling Supports Potential Biannual 50mg Dosing Regimen in Addition to Quarterly 25mg Dosing Regimen

- Plan to generate TTR reduction and safety data in patients receiving 50mg q6M to support sNDA to add biannual dosing regimen aligned with FDA input
- Expect start of q6M dosing study in **early 2021**

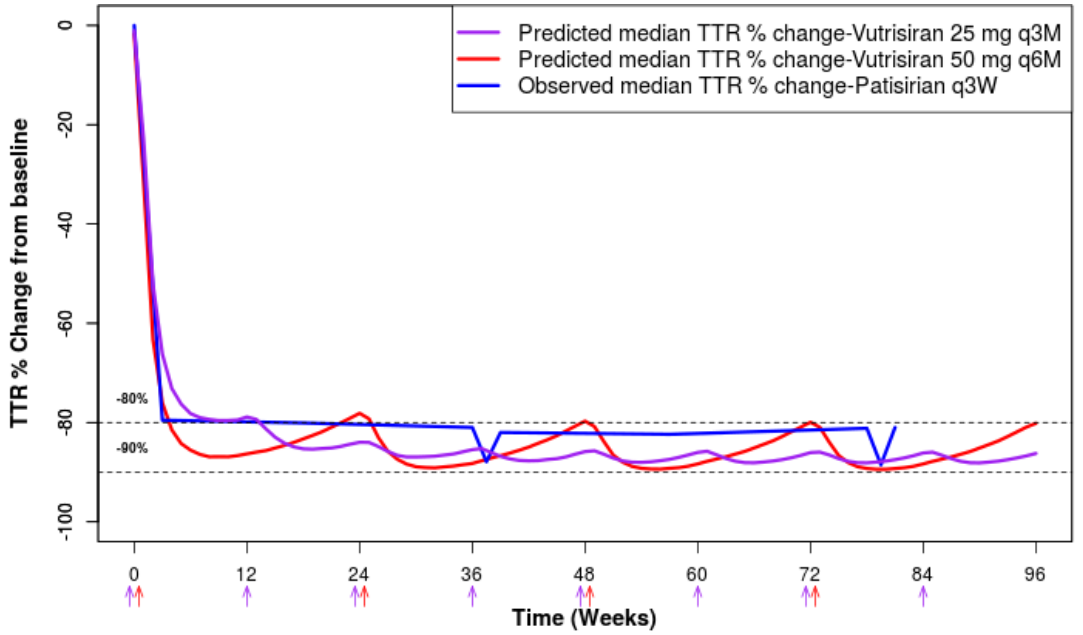
Phase 1 Study – Healthy Volunteers

- Mean max TTR reduction of >80% after single dose of either 25mg or 50mg†



Pharmacodynamic Modeling

- After repeat dosing, ~90% peak TTR reduction predicted with both 25mg q3M and 50mg q6M vutrisiran regimens

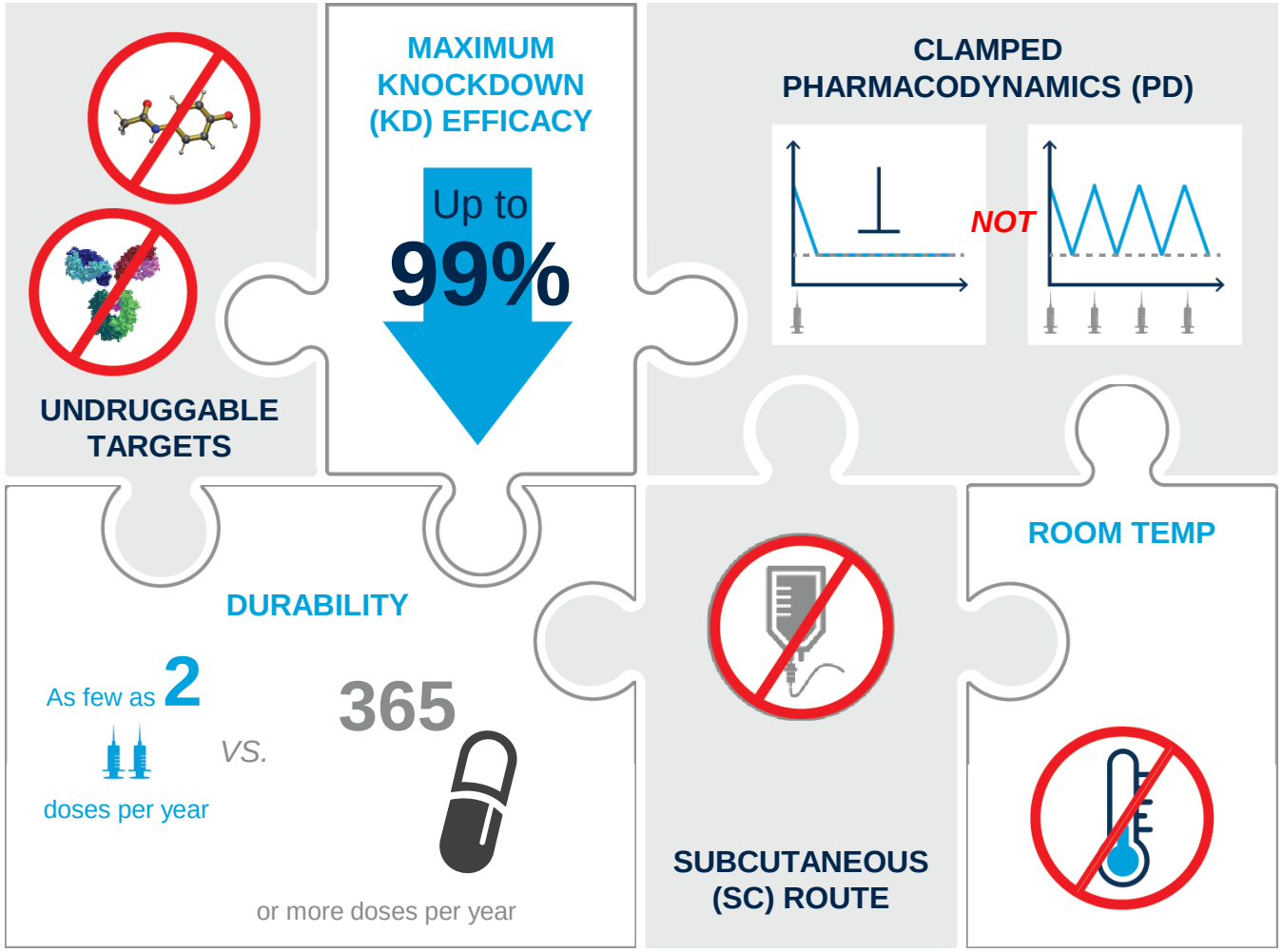


† Taubel J, et al. Phase 1 Study of ALN-TTRsc02, a Subcutaneously Administered Investigational RNAi Therapeutic for the Treatment of Transthyretin-Mediated Amyloidosis. ISA 2018: XVIIth International Symposium of Amyloidosis; Kumamoto, Japan; March 2018 (poster)

q3M – dosing every three months
q6M – dosing every six months

Key Features of Alnylam RNAi Therapeutics

Platform Profile Well-Suited for Large Indications



Alnylam RNAi Platform

- Infrequent, subcutaneous administration creates dosing flexibility for patients and eases treatment burden
  - Potential for quarterly and biannual dosing
- Wide therapeutic index with potential for transformative outcomes
- Extensive human safety experience across multiple indications, including large market indications such as hypercholesterolemia

Robust Commercial Platform Supports Expansion to Large Indications

RARE

ONPATTRO-PN
GIVLAARI
OXLUMO
Vutrisiran-PN

Fitusiran
ALN-AAT02
ALN-APP
ALN-HTT

SPECIALTY

ONPATTRO-CM
Vutrisiran-CM
Cemdisiran

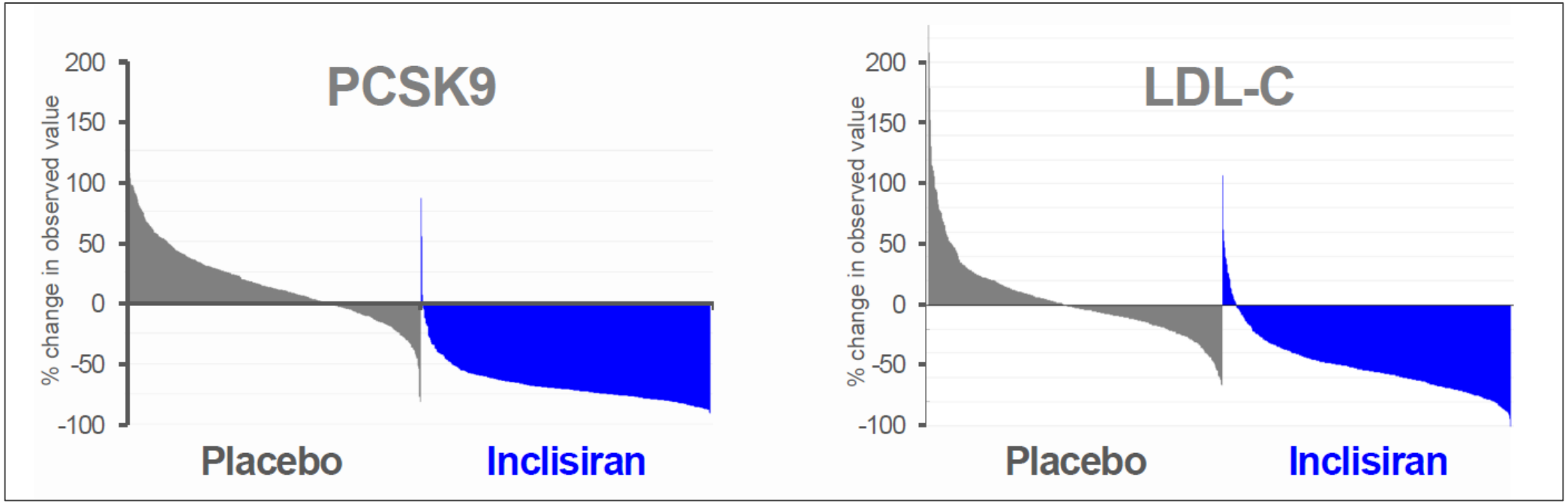
PREVALENT

Leqvio® (inclisiran)
ALN-HBV02 (VIR-2218)
ALN-AGT
ALN-HSD

ORION-11: Efficacy

Potent, Consistent Response to Inclisiran

Individual patient responses contributing to primary endpoint – 17 months

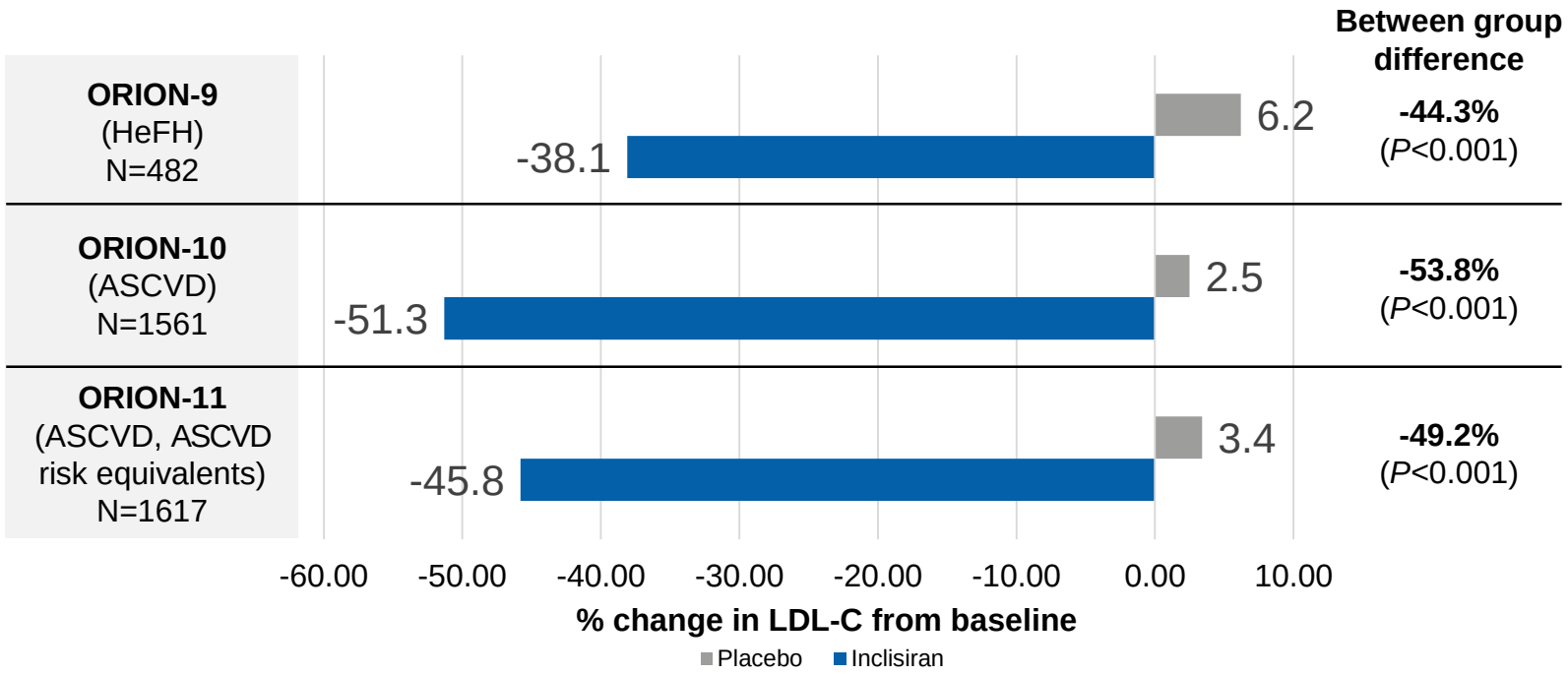


Ray KK, et al. N Engl J Med. 2020;382(16):1507-1519

Phase 3 ORION-9, -10, and -11

Primary Endpoint: Differential Time-Adjusted LDL-C Percentage Change After Day 90 and up to Day 540

Significant reductions in LDL-C percent change with inclisiran vs placebo on top of maximally tolerated statin dose after Day 90 and up to Day 540 (range, -44.3% – -53.8%)

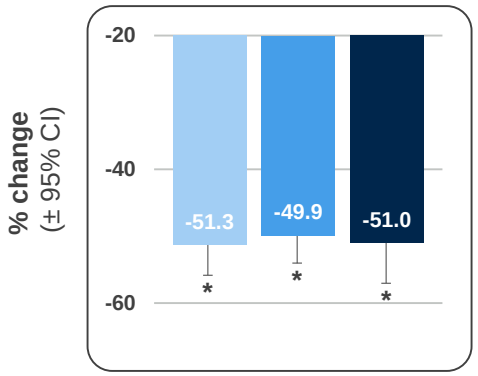


[1] Raal FJ, et al. N Engl J Med. 2020;382(16):1520-1530.
[2] Ray KK, et al. N Engl J Med. 2020;382(16):1507-1519.

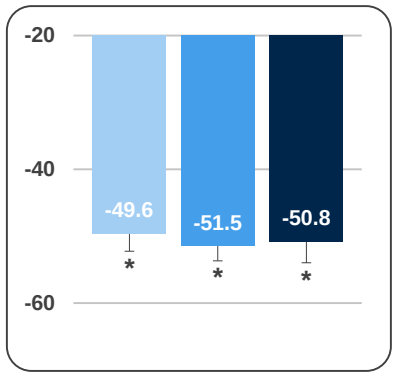
ORION Phase 3 Pooled Analysis

Sustained LDL-C Reduction at 17 Months Regardless of Age[1] or Gender[2]

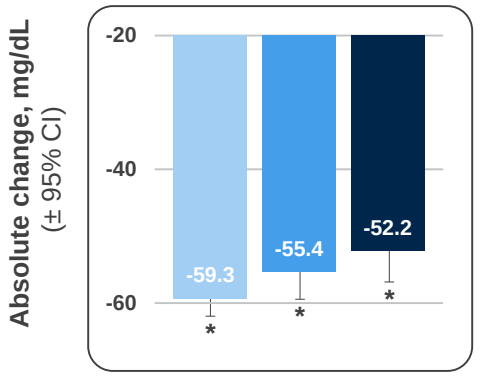
Change from Baseline to Day 510



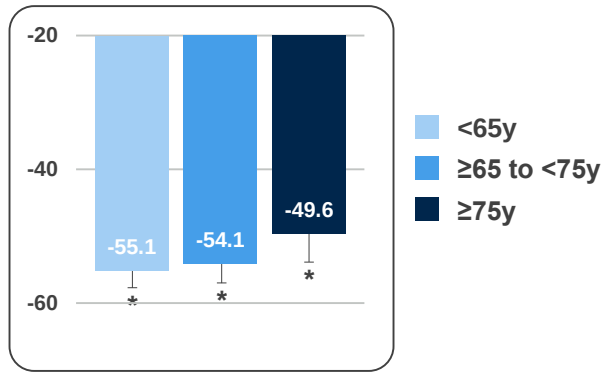
Time-Adjusted Change from Baseline After Day 90 to Day 540



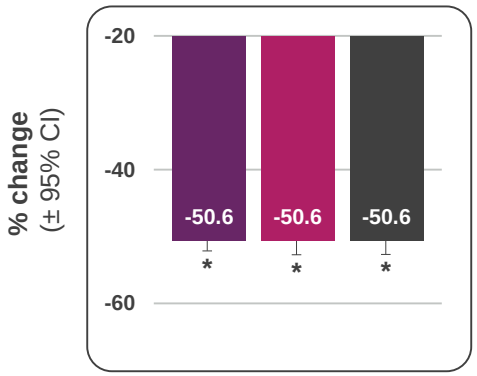
Change from Baseline to Day 510



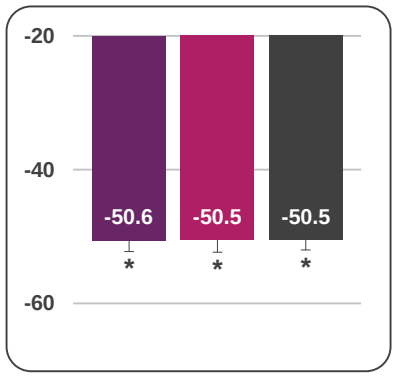
Time-Adjusted Change from Baseline After Day 90 to Day 540



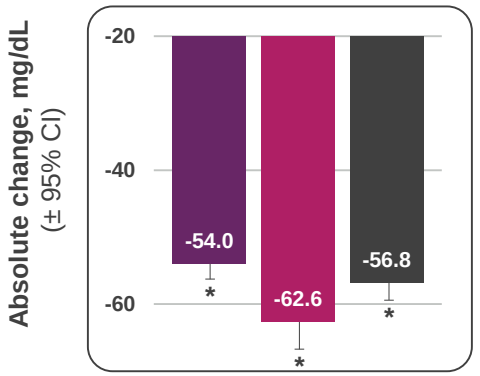
Change from Baseline to Day 510



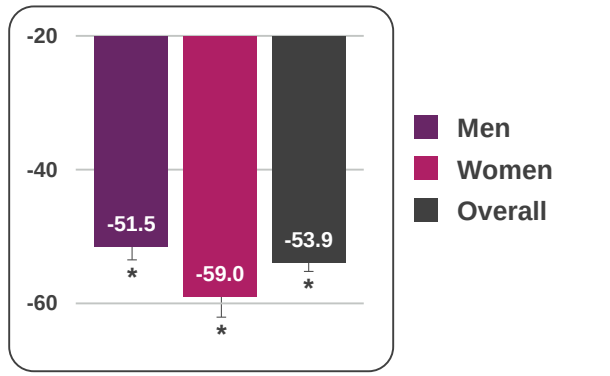
Time-Adjusted Change from Baseline After Day 90 to Day 540



Change from Baseline to Day 510



Time-Adjusted Change from Baseline After Day 90 to Day 540



[1] Wright RS, et al. Efficacy and Safety of Inclisiran According to Age: A Pooled Analysis of Phase III Studies (ORION-9, -10, and -11); Poster 2250. AHA 2020

[2] Wright RS, et al. Efficacy and Safety of Inclisiran According to Sex: A Pooled Analysis of the ORION-9, -10, and -11 Trials; Poster 2253. AHA 2020

* Placebo-corrected P<0.0001; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol

What is the Safety Profile of Inclisiran?

- Inclisiran was well-tolerated with a **safety profile similar to placebo** in the current evidence at hand[1,2]
- The **safety profile** of inclisiran has been informed in **more than 3500 patients** by a comprehensive clinical development program including 3 confirmatory phase 3 studies: ORION-9, -10, and -11[1,2]
- Treatment-related AEs were **similar** in both groups with the **exception of injection site reactions** that were more frequent in the inclisiran group. Those were predominantly mild; **none were severe or persistent**[1,2]
- SAEs and AEs leading to **discontinuation** were also **balanced among both arms**[1,2]
- The ongoing **cardiovascular outcomes trial** (ORION-4, approx. 15,000 patients) and data from open-label extension trials of the phase 3 program (ORION-3 and ORION-8) will provide additional information on the **long-term safety** profile[3-5]

[1] Raal FJ, et al. N Engl J Med. 2020;382(16):1520-1530. [2] Ray KK, et al. N Engl J Med. 2020;382(16):1507-1519.
[3] NCT03705234. https://www.clinicaltrials.gov/ct2/show/NCT03705234?term=ORION-4&draw=2&rank=1. Accessed October 20, 2020
[4] NCT03060577. https://www.clinicaltrials.gov/ct2/show/NCT03060577?term=ORION-3&draw=2&rank=1. Accessed October 20, 2020.
[5] NCT03814187. https://clinicaltrials.gov/ct2/show/NCT03814187. Accessed October 20, 2020.

Agenda

Progress to Date

Evolving the Pipeline

Future Outlook

Alnylam Early Stage Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

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

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

[1] POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics
[3] Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development

As of December 2020

Over 20 Preclinical Programs in Four Tissues Feeding Pipeline

LIVER

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

Alnylam/Regeneron
- ALN-HSD
- ALN-PNP
- ALN-REGN-L2
- ALN-REGN-L4
- ALN-REGN-L5

CNS

Alnylam/Regeneron
- ALN-APP
- ALN-HTT
- ALN-REGN-C3
- ALN-REGN-C4
- ALN-REGN-C5
- ALN-REGN-C6
- ALN-REGN-C7
- ALN-REGN-C8
- ALN-REGN-C9

EYE

Alnylam
- ALN-TTRoc

Alnylam/Regeneron
- ALN-REGN-E1
- ALN-REGN-E2
- ALN-REGN-E3
- ALN-REGN-E4

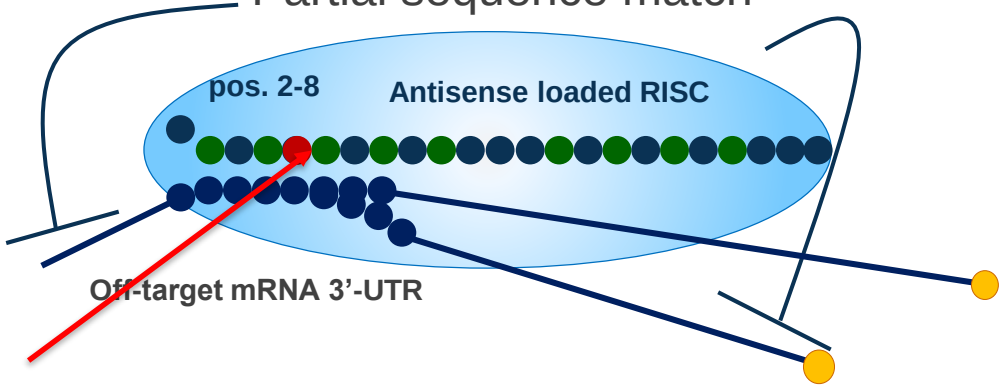
LUNG

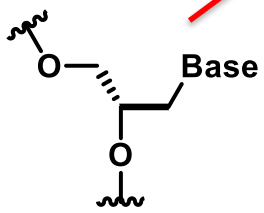
Alnylam/Vir
- ALN-COV
- ALN-VIR2 (ACE2)
- ALN-VIR3 (TMPRSS2)

ESC+ Seed Pairing Destabilization Strategy Improved Specificity and Therapeutic Index in Rats

Off-target binding

Partial sequence match



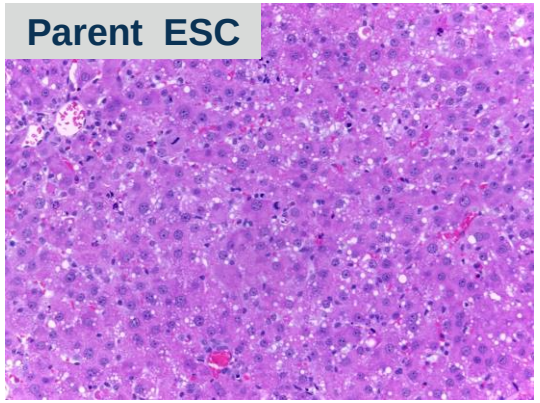


(*S*)-GNA

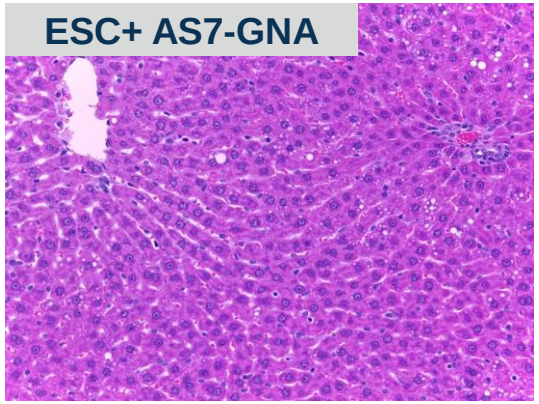
Unde[illegible]d off-target activity

Rat Liver Histopath for 30 mg/kg dose

Parent ESC



ESC+ AS7-GNA



Important Considerations

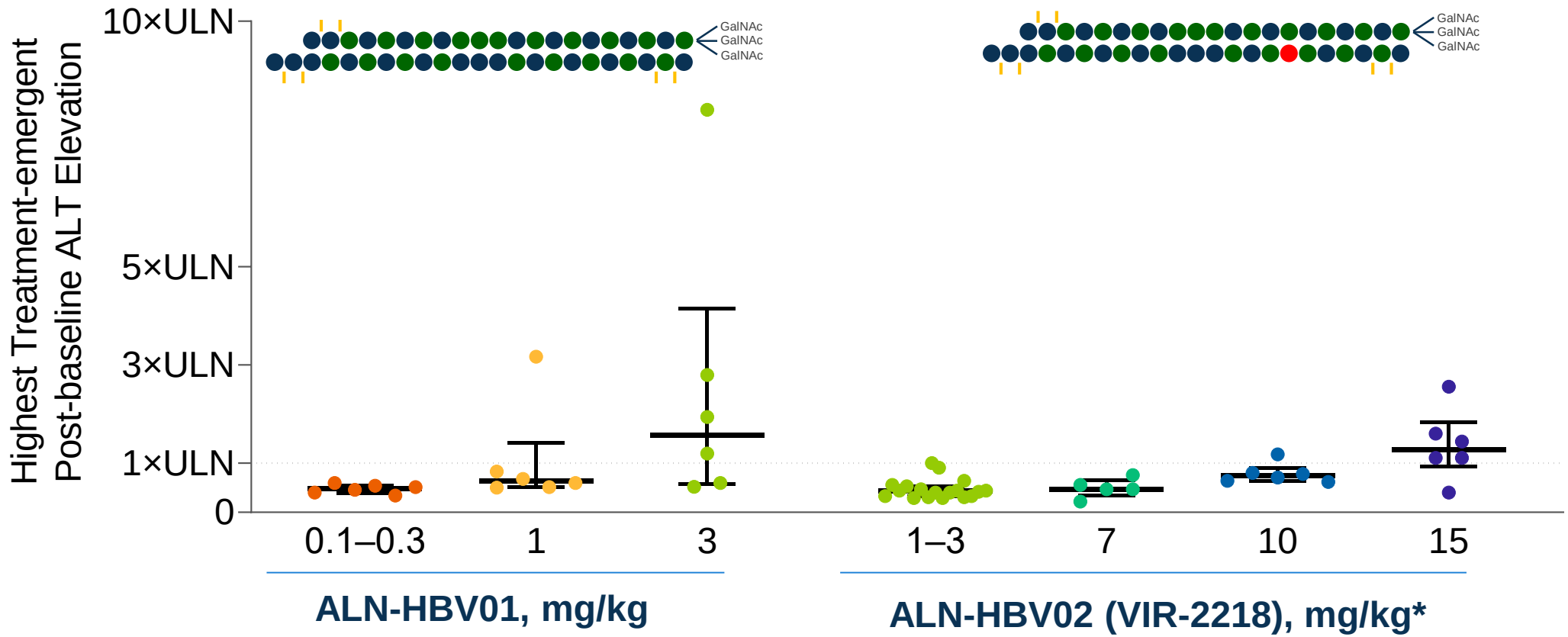
1. On-target potency must be maintained *in vivo*
2. Off-target activity should be minimized

How would ESC+ design translate in humans?

- Evaluated ESC+ versions of ALN-HBV and ALN-AAT01

Bramsen et. al. *Nucleic Acids Res*. **2010**
Vaish et. al. *Nucleic Acids Res.* **2011**
Lee et. al. *Nat. Comm.* **2015**
Janas, Schlegel et al. *Nat. Comm.* **2018**

Human: Treatment-Emergent Post-Baseline ALT Elevations in Healthy Volunteers with Normal ALT at Baseline

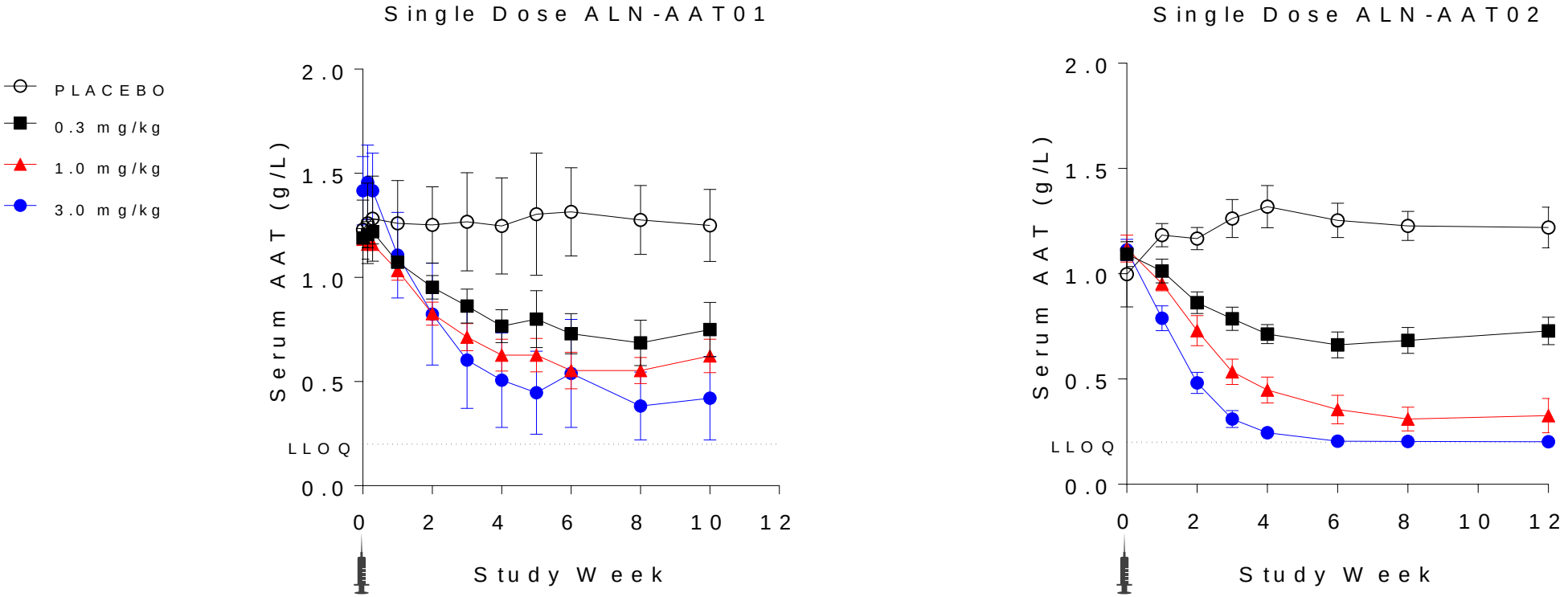


- No post-baseline ALT elevations to >ULN in ALN-HBV02 (VIR-2218) or ALN-HBV01 cohorts were associated with increases in bilirubin >ULN
- No changes in functional status of liver (e.g., albumin, coagulation parameters) or clinical signs/symptoms of hepatic dysfunction were observed in any ALN-HBV01- or ALN-HBV02 (VIR-2218)-treated patient

* Approximate mg/kg dose based on an average adult weight of 60 kg; fixed doses ranged from 50–900 mg. ULN, upper limit of normal.

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

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

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.

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

Investing in Next Wave of Genetically Validated Targets

Expanding Alnylam Leadership in Genetics

biobank uk

THE UNIVERSITY OF CALIFORNIA
LET THERE BE LIGHT
UCLA

REGENERON

- **Larger, statistically powered datasets**
- **Novel genetically validated targets**
- **Increased ethnic and health diversity**
- **Target safety validation**

Heterozygous LOF in XDH Protects from Gout

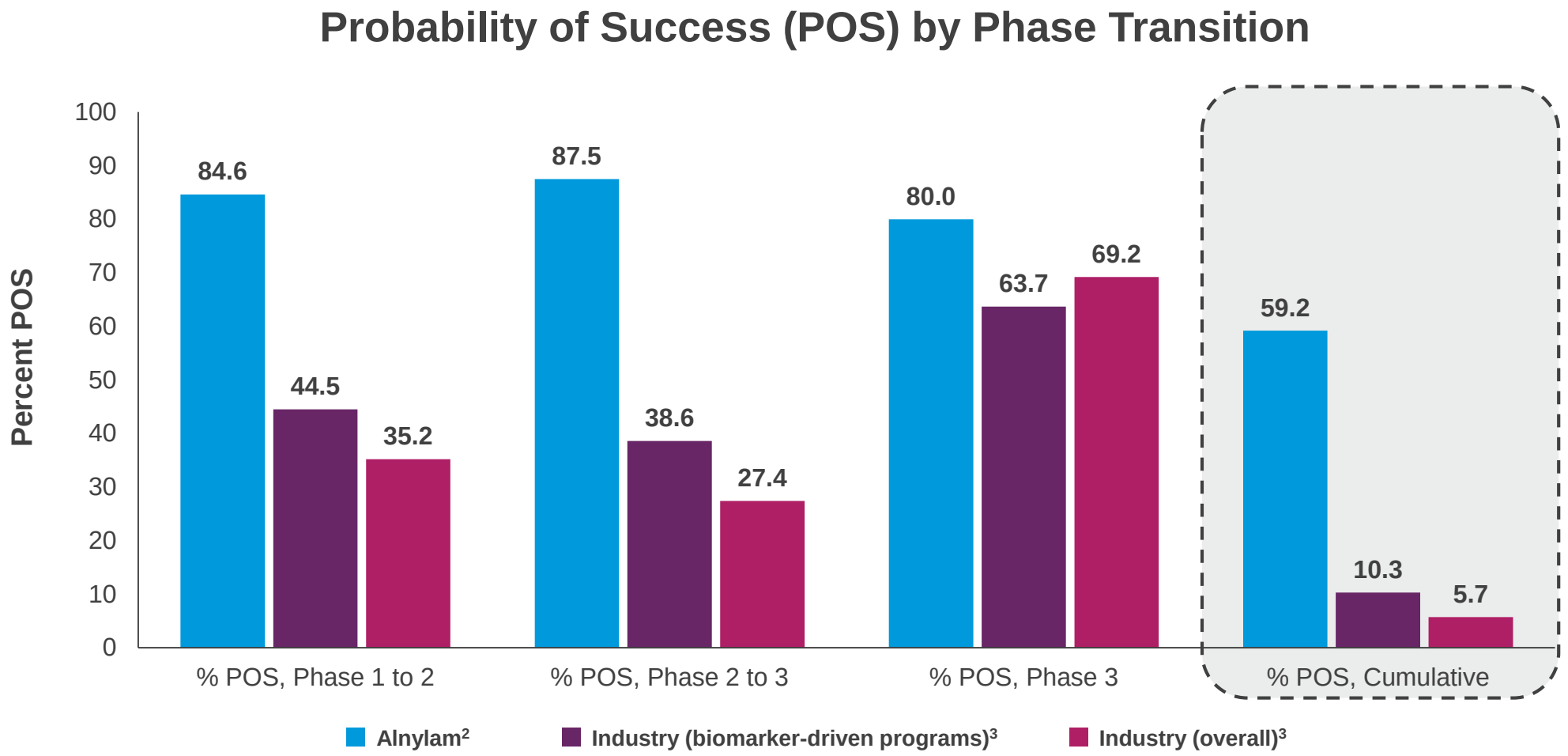
~50% reduction in XDH associates with ~40% reduction in risk of gout

Gene variant set	XDH LOF
Phenotype	Gout
P-value	0.008
Effect (95% CI)	0.62 Odds Ratio (0.44 – 0.88)
N carriers	1549
N observed/N expected	33/51

Gout defined using ICD10 M10 in hospital, death and primary care data (CDHP_41065_v2)

Productivity of Alnylam RNAi Therapeutic Platform

Comparison of Historical Industry Metrics to Alnylam Portfolio[1]



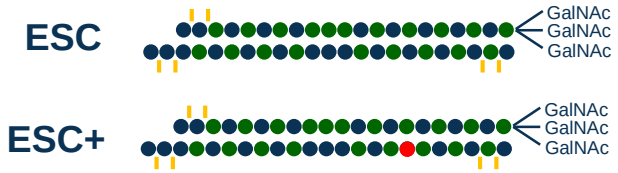
[1] Past rates of Alnylam and industry respectively may not be predictive of the future

[2] Alnylam programs biomarker-driven at all stages of development (100%); figures include ALNY-originated molecules now being developed by partners

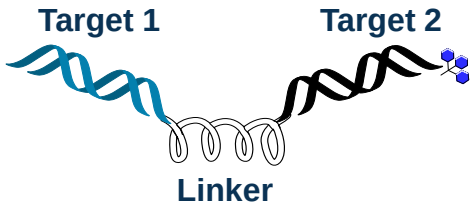
[3] Wong et al., Biostatistics (2019) 20, 2, pp. 273–286

RNAi Platform Advances

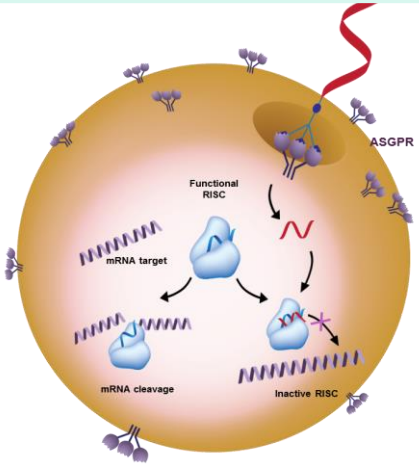
ESC+ Design: Improved Specificity and Safety in Humans



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



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



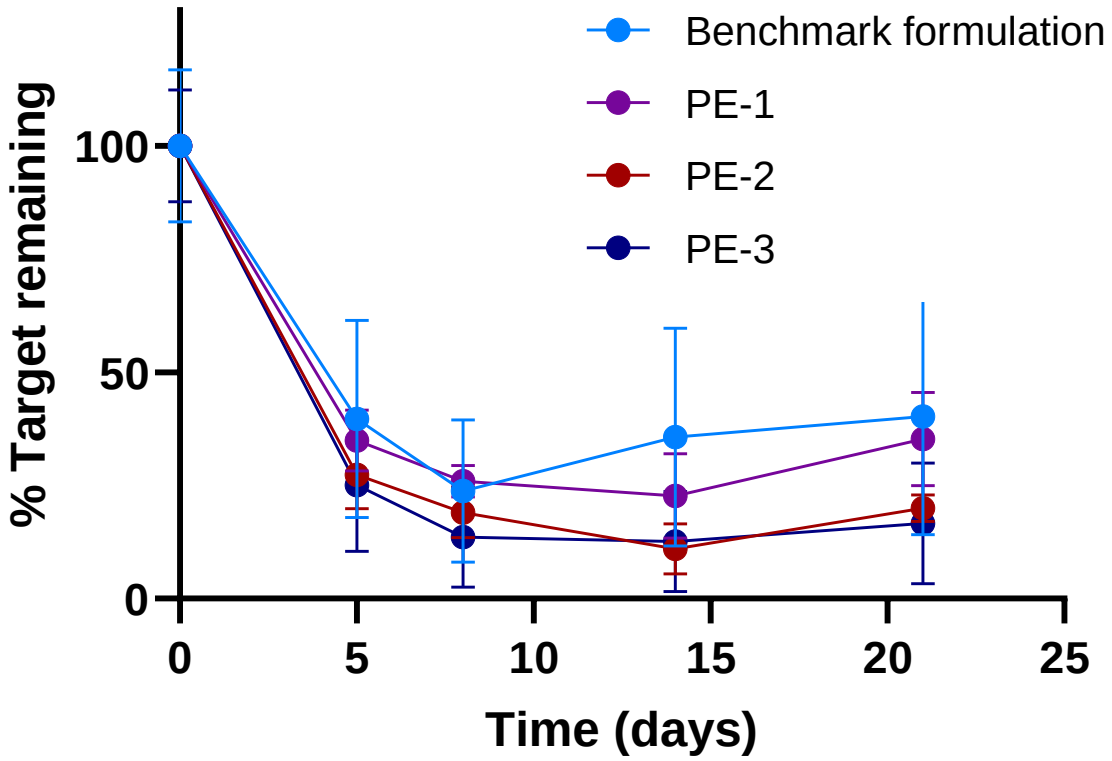
Extrahepatic Delivery: RNAi Rx for CNS and Ocular Diseases

Oral Delivery

Oral Delivery of RNAi

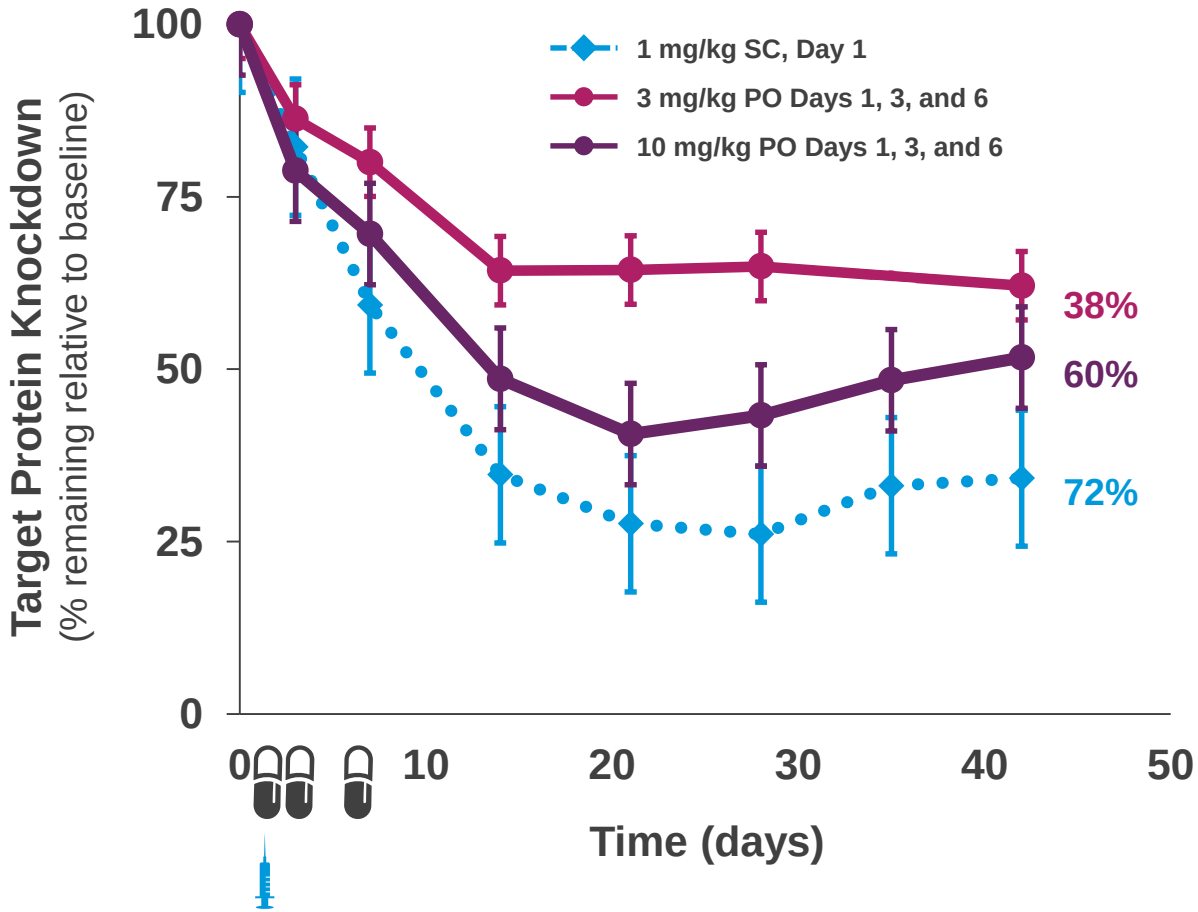
Dose Dependent, Durable Knockdown Similar to Subcutaneous Dosing

New Permeation Enhancers Improve Oral Delivery of GalNAc-siRNA in Mice



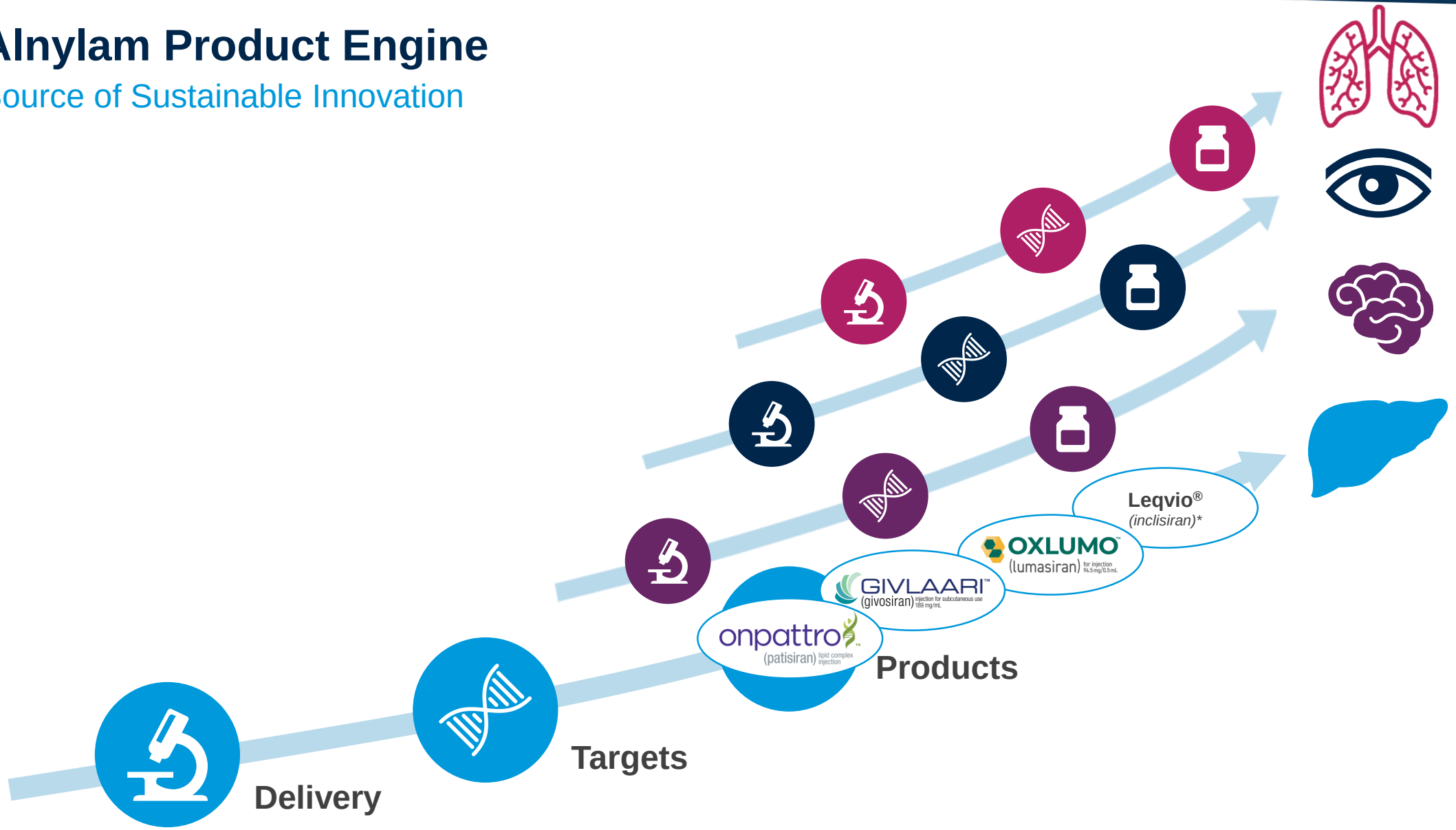
PO 1 x 10 mg/kg

Achieved PoC for Oral Delivery in NHP



Alnylam Product Engine

Source of Sustainable Innovation



2006 | 2011 | 2018 | 2020 | 2020-30

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

VOICES OF **PATIENTS & CAREGIVERS**

“My son is 5 years post-transplant and he is still suffering from so much oxalate in his system from before the transplant. He has oxalate crystals in his eyes and they said it is in his brain and in his bones and in other organs.”

Caregiver of two pediatric patients diagnosed with PH1

Alnylam® PHARMACEUTICALS

ATTR amyloidosis – now and the future

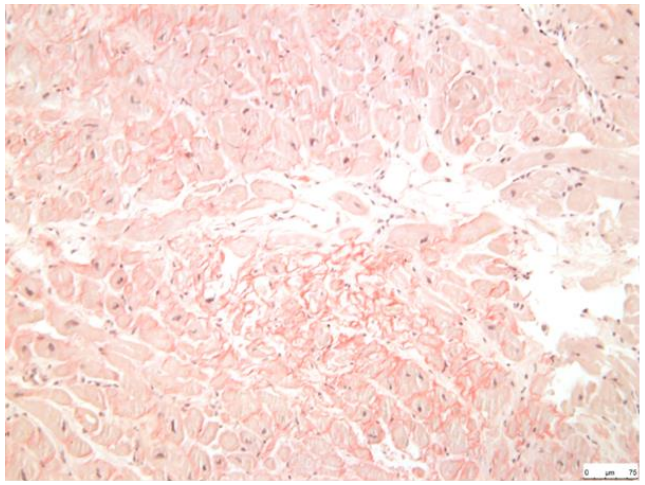
Professor Philip Hawkins
National Amyloidosis Centre
Royal Free Hospital
University College London, UK

UCL

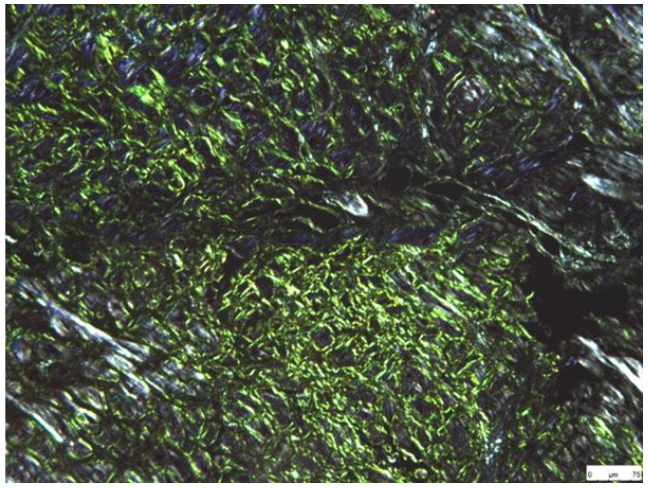
NHS
Royal Free London
NHS Foundation Trust

Amyloid – the disease causing entity

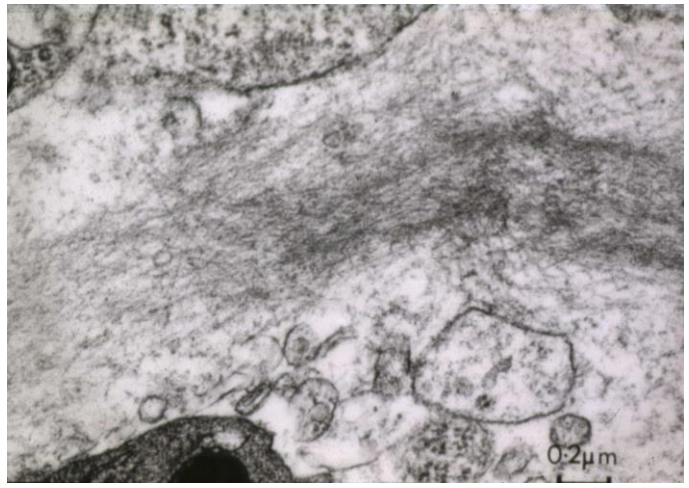
- Deposits of misfolded, aggregated protein as insoluble fibres in tissues, which disrupt the structure and function of vital organs
- Many types, mostly very rare: transthyretin (ATTR amyloid) the most common
- Identifiable through Congo red staining of a biopsy sample, producing green birefringence under polarized light



Congo red stain

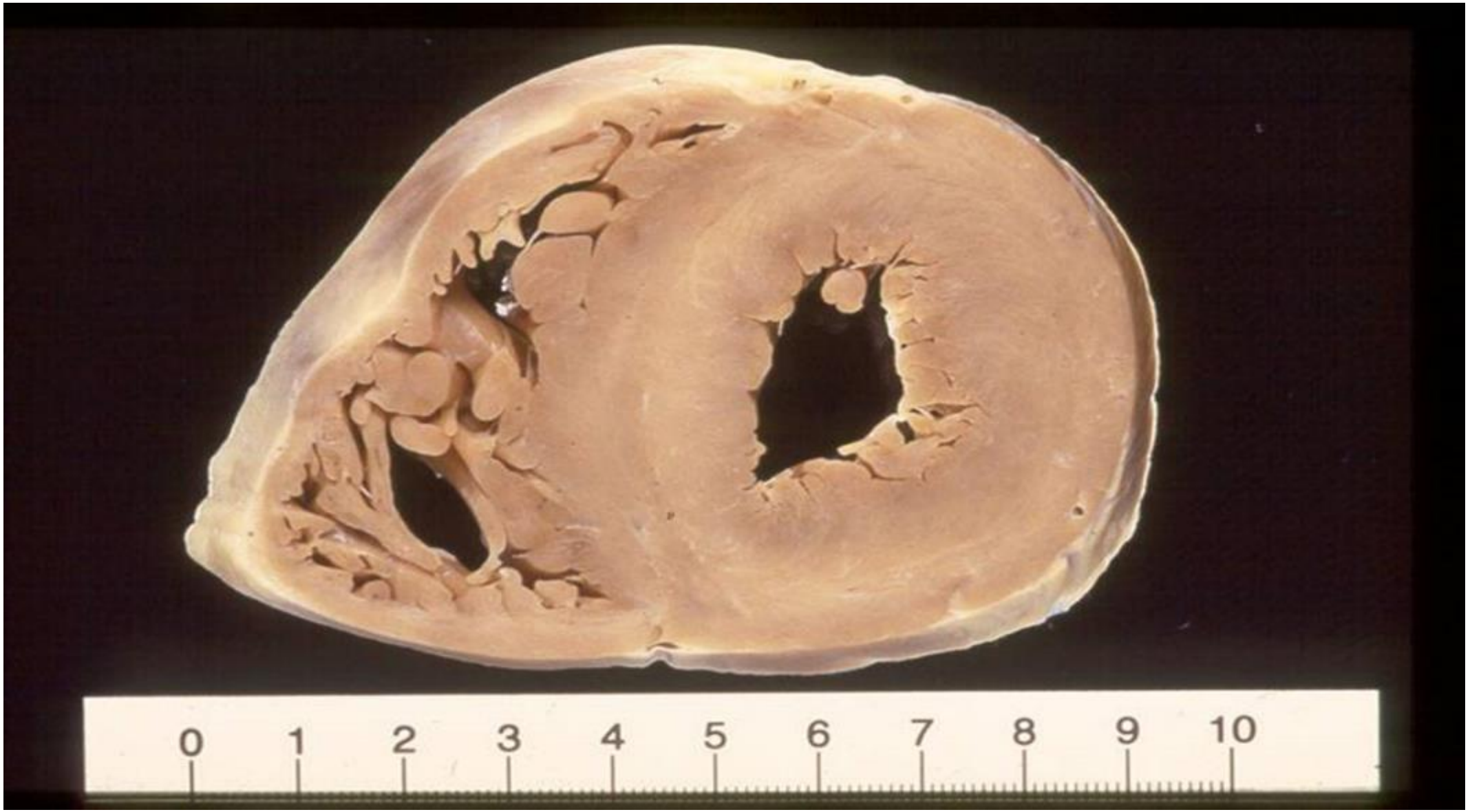


Under polarized light



Electron microscopy

Cardiac ATTR amyloidosis – the size of the problem



Wild-type (non-hereditary) ATTR amyloidosis

Amyloid protein is normal, unmutated, transthyretin (TTR), produced in the liver

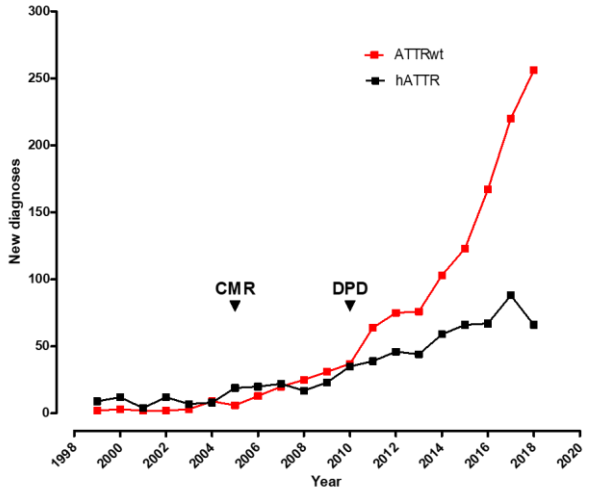
Predominantly a cardiomyopathy

- Increasingly recognised cause of heart failure in individuals >50 yrs, mostly > 70 yrs,~90% men
- Progressive and fatal with 2-10 years
- Prior symptoms of ATTR include carpal tunnel syndrome in most, ~5-10 yrs before heart failure
- Autopsies shown cardiac ATTR amyloid deposits in **~25% over 85 years**
- Historically very few patients diagnosed whilst alive
  - ➢ Poor specificity of echocardiography; looks like LVH

69 year old Caucasian gentleman
3 year history of dyspnoea, fatigue
Echocardiogram – thickened heart walls (21mm), restrictive physiology
Endomyocardial biopsy – amyloid (referred to NAC)
Immunohistochemistry – ATTR amyloid
TTR gene sequence – wild-type

- Final diagnosis – **wild-type ATTR amyloidosis**
- No disease-modifying treatment

The <u>only</u> new diagnosis of wild-type ATTR amyloidosis in 2000!

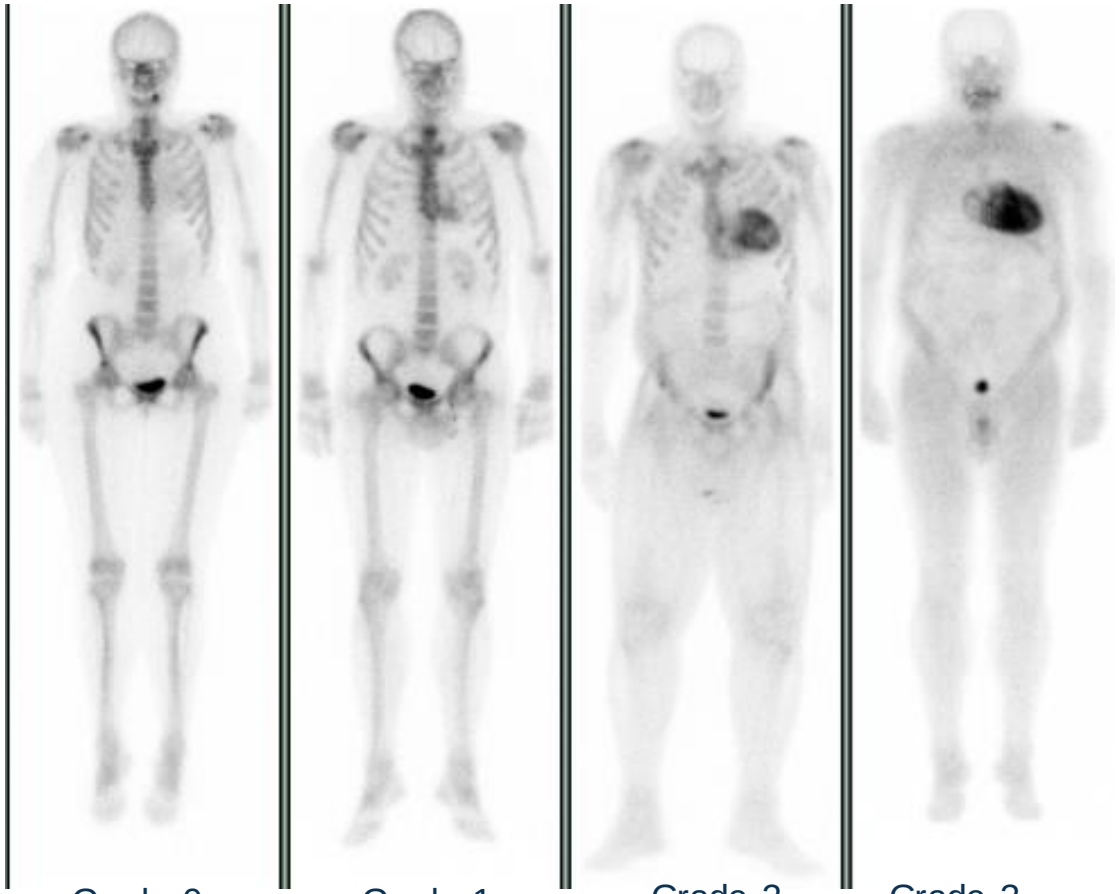


New diagnoses of ATTR-CM in UK

Lane T *et al,* Circulation 2019;140:16–26

Identification of cardiac ATTR amyloid using repurposed DPD/PYP bone scintigraphy

Tc-labeled DPD/PYP Scintigraphy

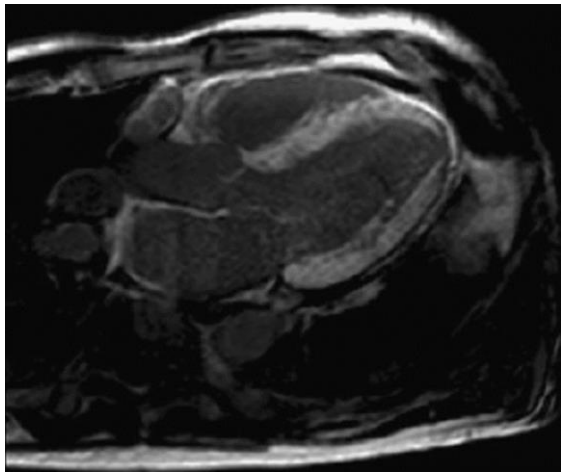


- Mechanism unclear, but extremely sensitive
- Cheap, widely available
- **Grade 2+** uptake in **all** ATTR-CM patients
- **Diagnostic of ATTR-CM** in conjunction with simple blood and urine tests to exclude possibility of AL amyloidosis
- NAC experience: DPD scans detects cardiac ATTR amyloid deposits at very early stage (Grade 1), before symptoms
- **Potential to identify early asymptomatic ATTR amyloid**

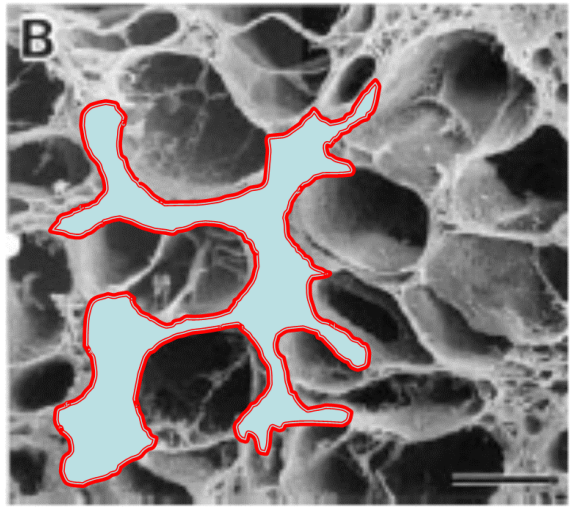
Rapezzi et al, JACC Imaging 2011:659-70
Hutt et al, Eur Heart J 2014;15:1289-1298
Gillmore JD *et al,* Circulation 2016;33:2404-12

Characterization of cardiac ATTR amyloid deposits by MRI (CMR)

- More accurate measurement of volume, mass and wall thickness than echo
- Enables myocardial tissue characterization
- Characteristic patterns of contrast enhancement (late gadolinium enhancement – LGE technique), indicative of amyloidosis
- T1 mapping enables measurement of **extracellular volume (ECV) ,** the compartment in which amyloid accumulates
- **Uniquely enables serial measurements of amyloid load in clinic and trials**



CMR showing gadolinium contrast throughout LV wall



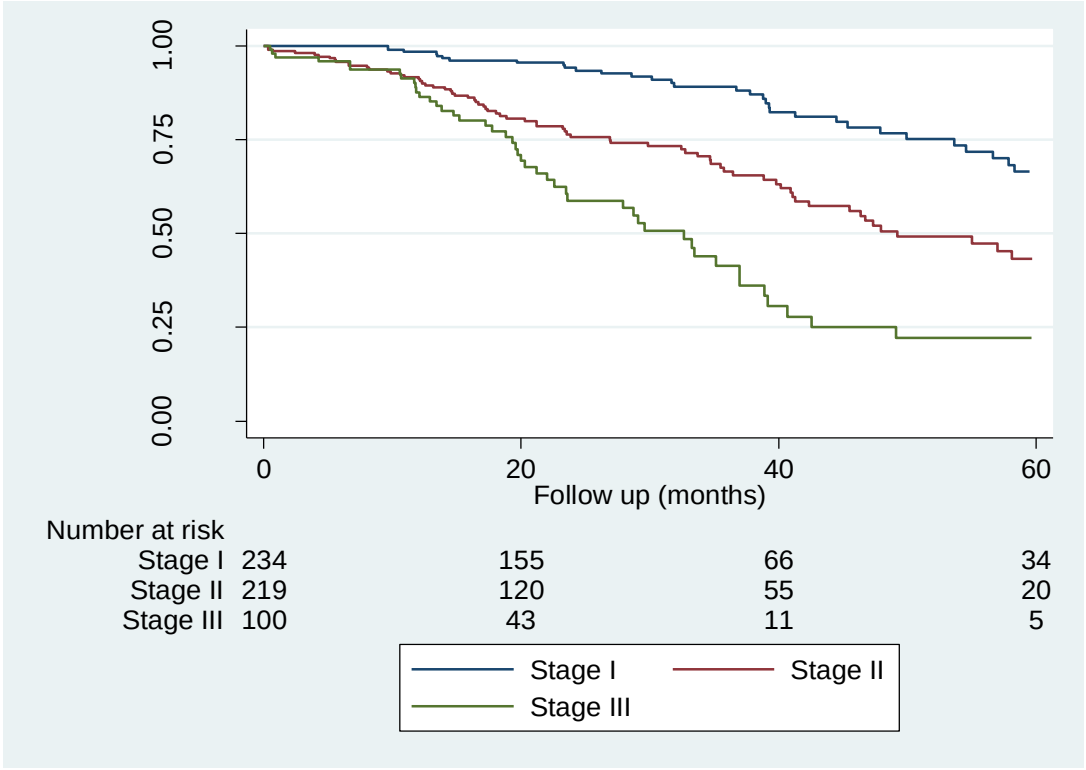
Electron micrograph showing much expanded ECV (shaded)

Normally ~30%
In ATTR ~60%

Martinez-Naharro A *et al.* J Am Coll Cardiol. 2017; 70:466-477

Staging cardiac ATTR amyloidosis – NAC system

Using cut-offs for NT-proBNP (>3000ng/L) & eGFR (<45ml/min): neither, one, both = stage 1, 2, 3

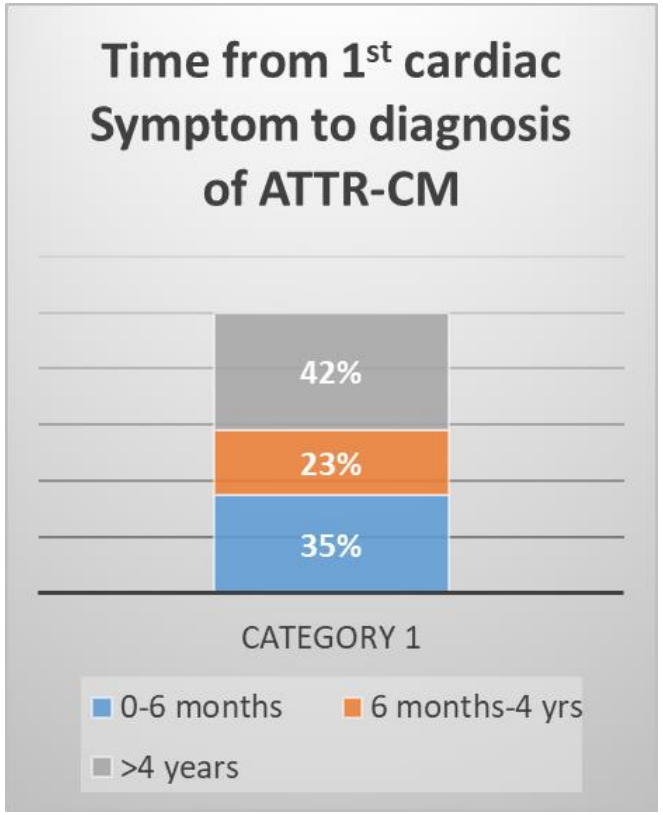


	Stage I	Stage II	P value	Stage III	P value	Harrell's C
Number (total = 553)	234 (42%)	219 (40%)		100 (18%)		
Median survival (months)	Indeterm-inable	49.2		32.7		
Cox regression: HR (95% CI)	1	2.26 (1.51–3.36)	<0.001	4.37 (2.80–6.83)	<0.001	0.70

- Median survival overall ~5 yr
- Progressive functional decline: reduction of ~50-100 m/yr on 6MWT
- Progressive rise in NT-proBNP of ~800-1200 ng/L/year
- Progressive decline in renal function due to reduced perfusion
- Rate of progression through NAC stages is further prognostic of survival

Gillmore JD *et al*, Eur Heart J 2018;39:2799–2806

Diagnostic delay in cardiac ATTR amyloidosis



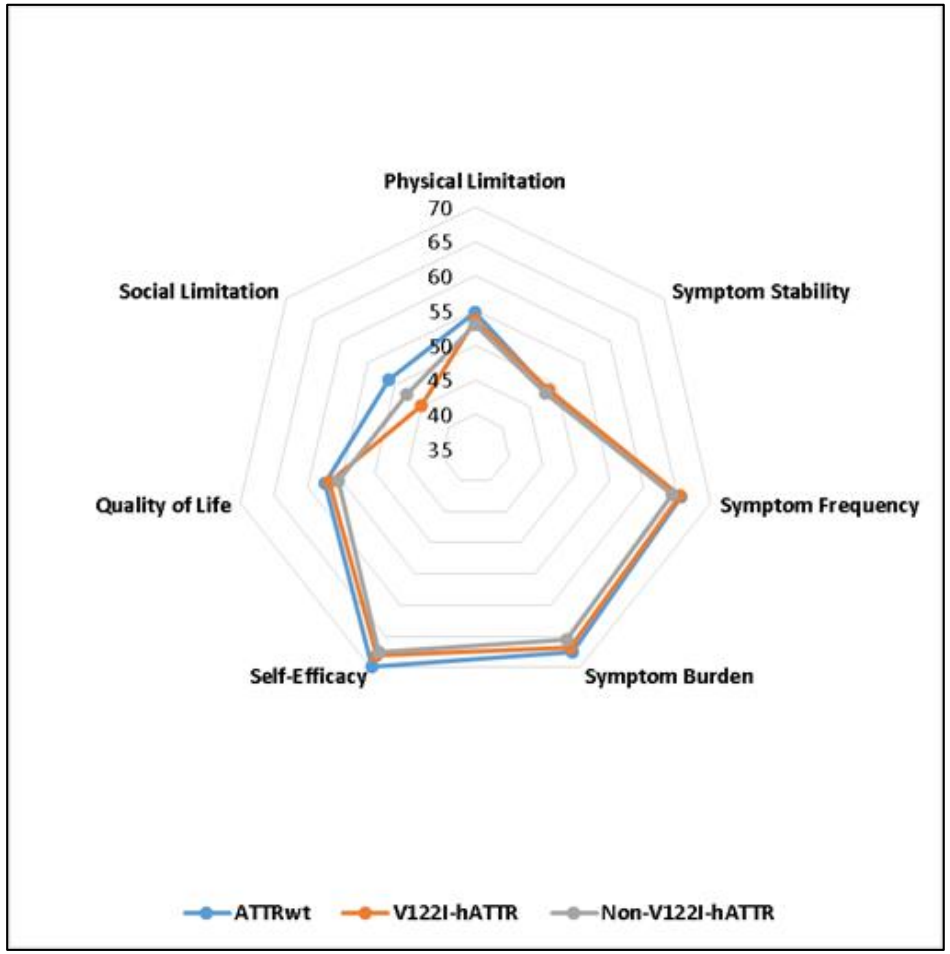
534 English patients with ATTR-CM with complete information for 3 years before diagnosis on NHS Hospital Episodes Statistics (HES) database (to 2016)

- Attended hospital a median 17 times
- Median of 3 hospital admissions
- Median diagnostic delay from first presentation with cardiac symptoms was 39 months
- 42% diagnosed >4 years after first presentation with cardiac symptoms
- Further 23% diagnosed 6 months to 4 years after first presentation

Lane *et al*, Circulation 2019;140:16-26
Lousada, *et al*. *JACC* 2018;71:11(Abstract)

Burden of Disease and Quality of Life in ATTR amyloidosis

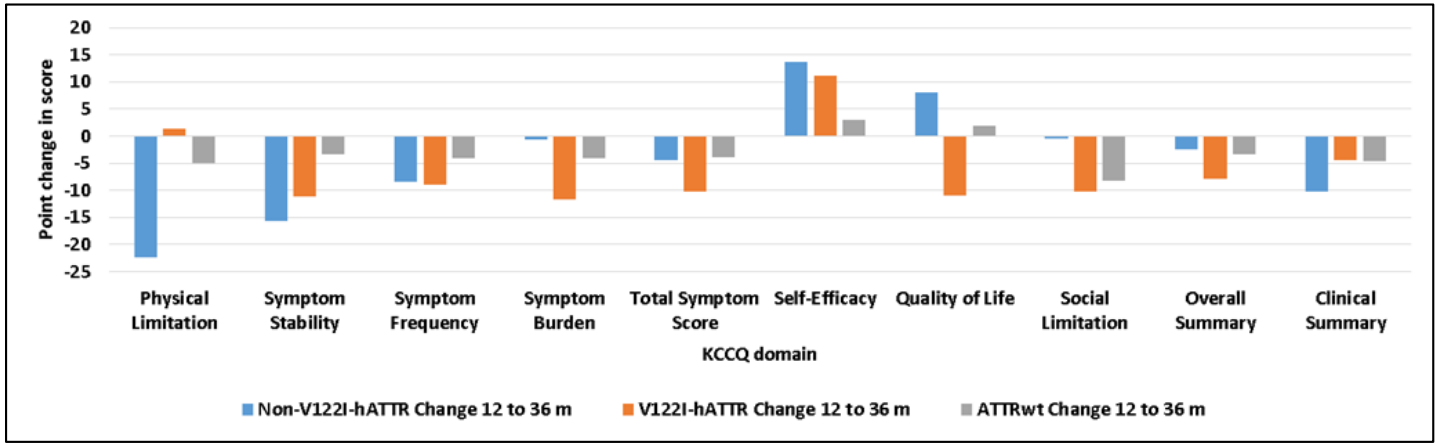
At diagnosis – healthy is 100



Health-related quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) in 158 patients @ NAC

- Patients have poor quality of life (QoL) at time of diagnosis of ATTR amyloidosis
- Caregivers also report substantial burden
- QoL worsens as ATTR amyloidosis progresses

Follow up: change from 12 to 36 months



Lane *et al,* Circulation 2019;140:16-26

Epidemiology of wtATTR amyloidosis

- True prevalence unknown, but evidently greater than previously thought; **2-300,000** worldwide?
- Data emerging that it is much overlooked in older people with:

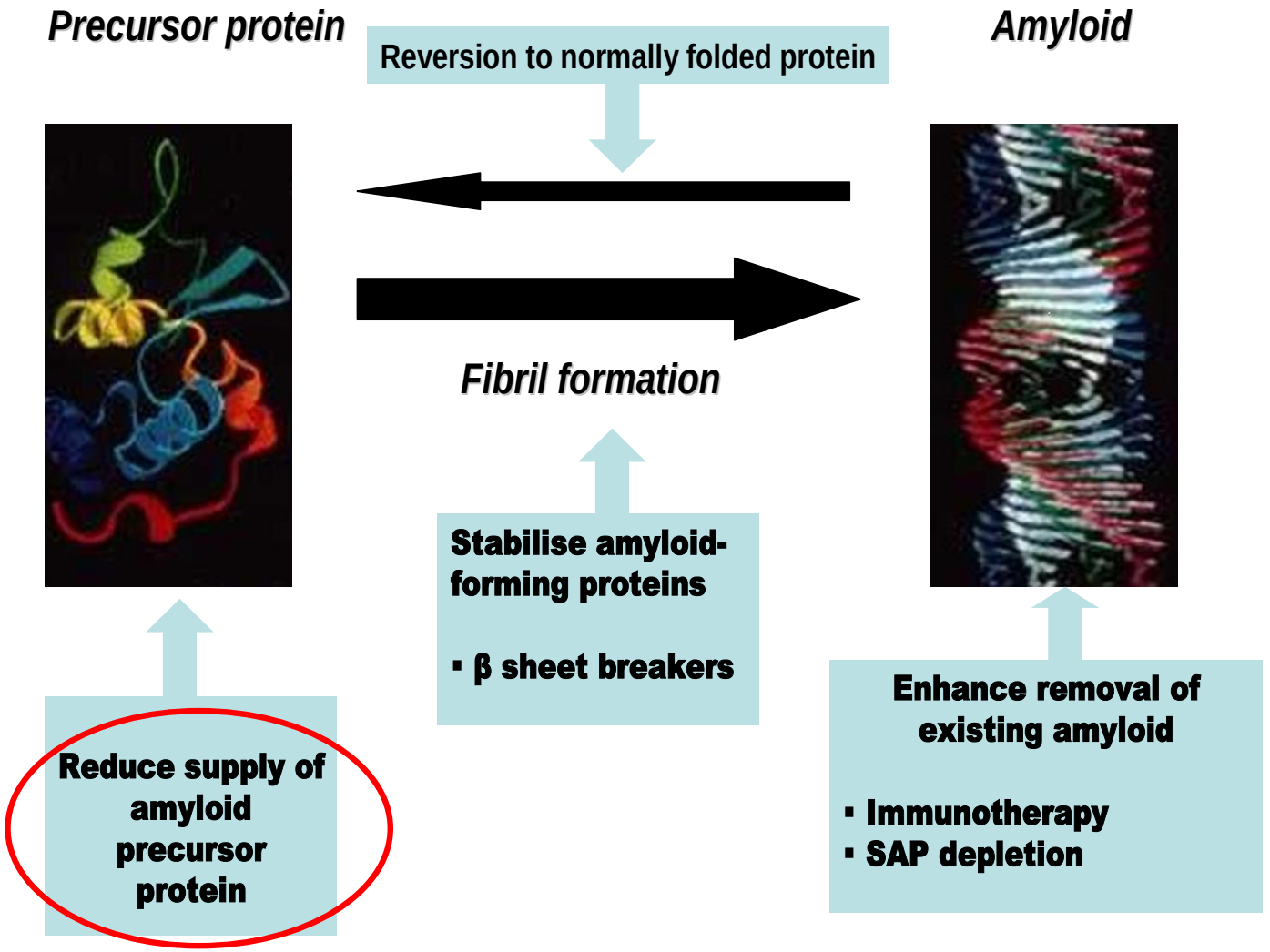
HFpEF	2.5 million	>65 years	in US	**>10% of those with 'LVH' on echo**
Aortic stenosis	2.7 million	>75 years	in US	**>10% of patients undergoing TAVR**
Atrial fibrillation	5 million	>65 years	in US	**Not studied yet**
Being over 85 yrs	7 million		in US	Autopsy data suggest some **500,000 people**

- Ongoing PYP / DPD studies will provide substantial data on prevalence of wtATTR by 2022

  Briani, Italy: IIS retrospective analysis of 10,000 patients who underwent bone scintigraphy (supported by Alnylam, Akcea, Pfizer)

  Four studies looking at **wtATTR in HFpEF**, three with corporate sponsors or funding (Gaggin / MGH IIS, NCT03414632, NCT04424914 and NCT04587648)

Treatment strategies in amyloidosis



Reducing the supply of the amyloid fibril precursor protein

Benefits of 'knock-down' in AA and AL amyloidosis are well established

More knock-down = better outcomes

AA

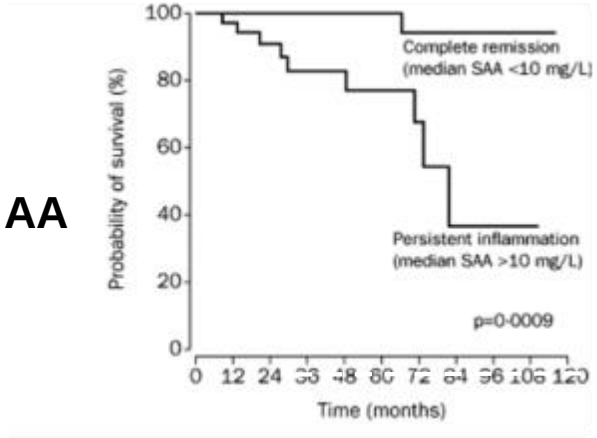
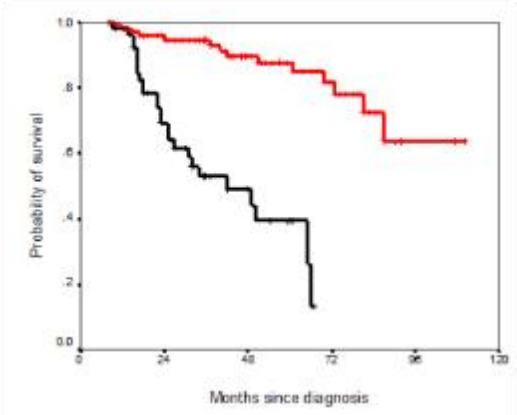


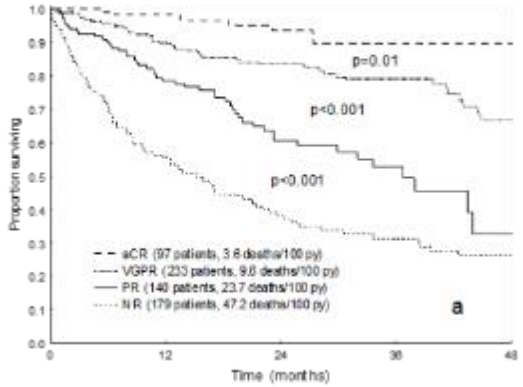
Table 3. Unadjusted Relative Risk of Death Associated with the Most Recent Median Annual SAA Concentration during Follow-up.*

SAA Octile (mg/liter)	Relative Risk (95% CI)	P Value
<4	1.0	
≥4 to <9	3.9 (1.5–10.4)	0.007
≥9 to <16.7	5.1 (2.7–9.4)	0.003
≥16.7 to <28	7.0 (3.7–13.4)	0.07
≥28 to <45.6	9.1 (4.8–17.2)	0.008
≥45.6 to <87	12.1 (6.9–21.4)	<0.001
≥87 to <155	17.0 (8.6–33.8)	<0.001
≥155	17.7 (8.7–36.0)	<0.001

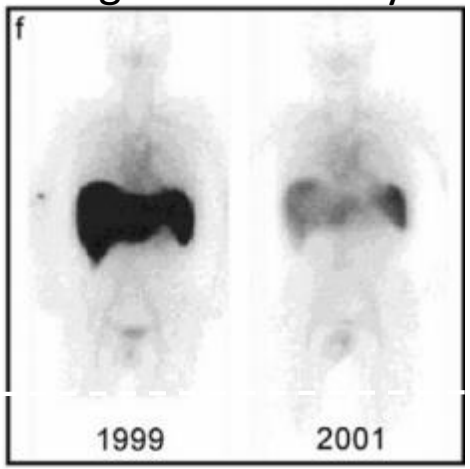
* The SAA value is the median concentration within each 12-month period and was incorporated into the Cox regression model as a time-dependent covariate.

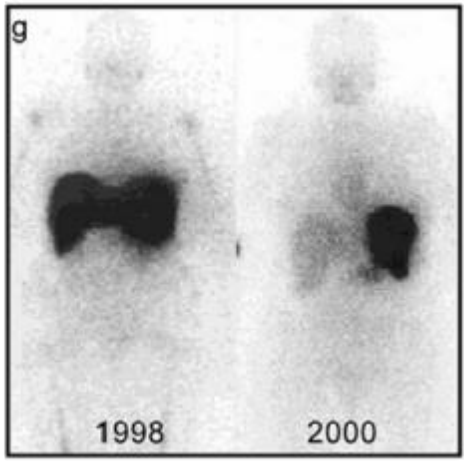
AL

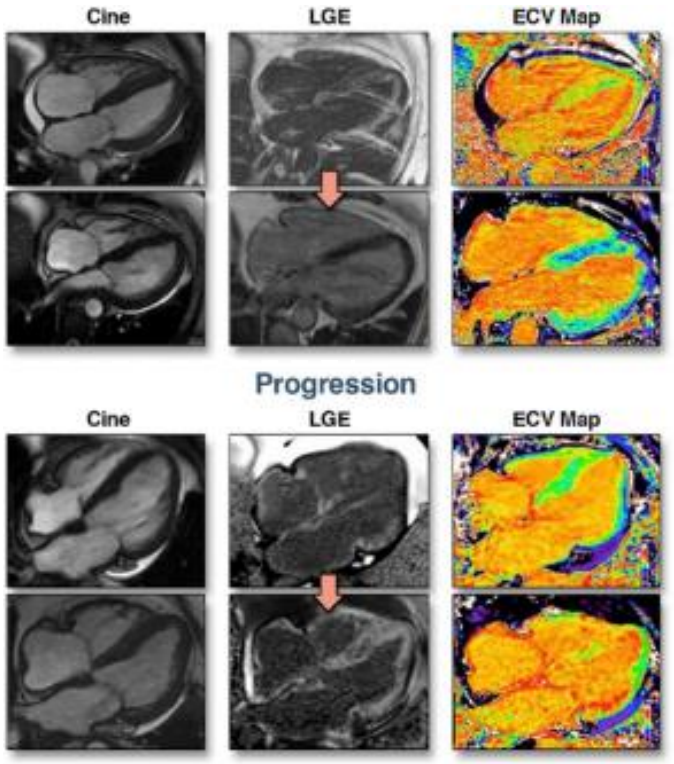




Regression of amyloid evident on SAP scan and CMR







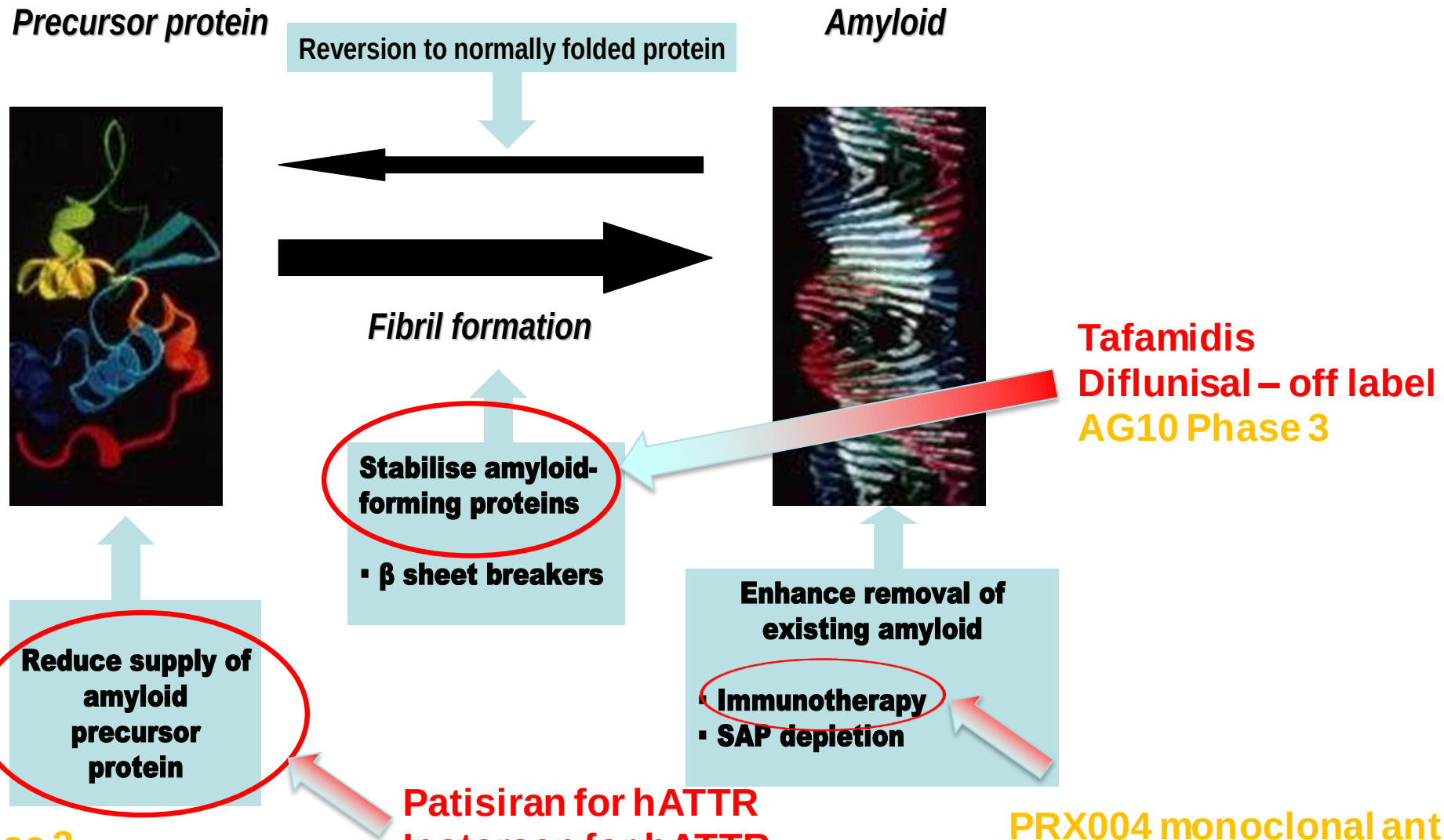
Survival, clinical benefit, and regression of AA and AL amyloid proportionate to degree of knock-down

Gillmore JD *et al*, Lancet 2001;358:24-29
Lachmann HJ *et al*, NEJM 2007:356;2361-71
Palladini G *et al*, JCO 2012;30:4541-4549
Martinez-Naharro A *et al*, JACC CV Imaging, 2018;11:152-154

Treatment strategies in (ATTR) amyloidosis

Available

In development



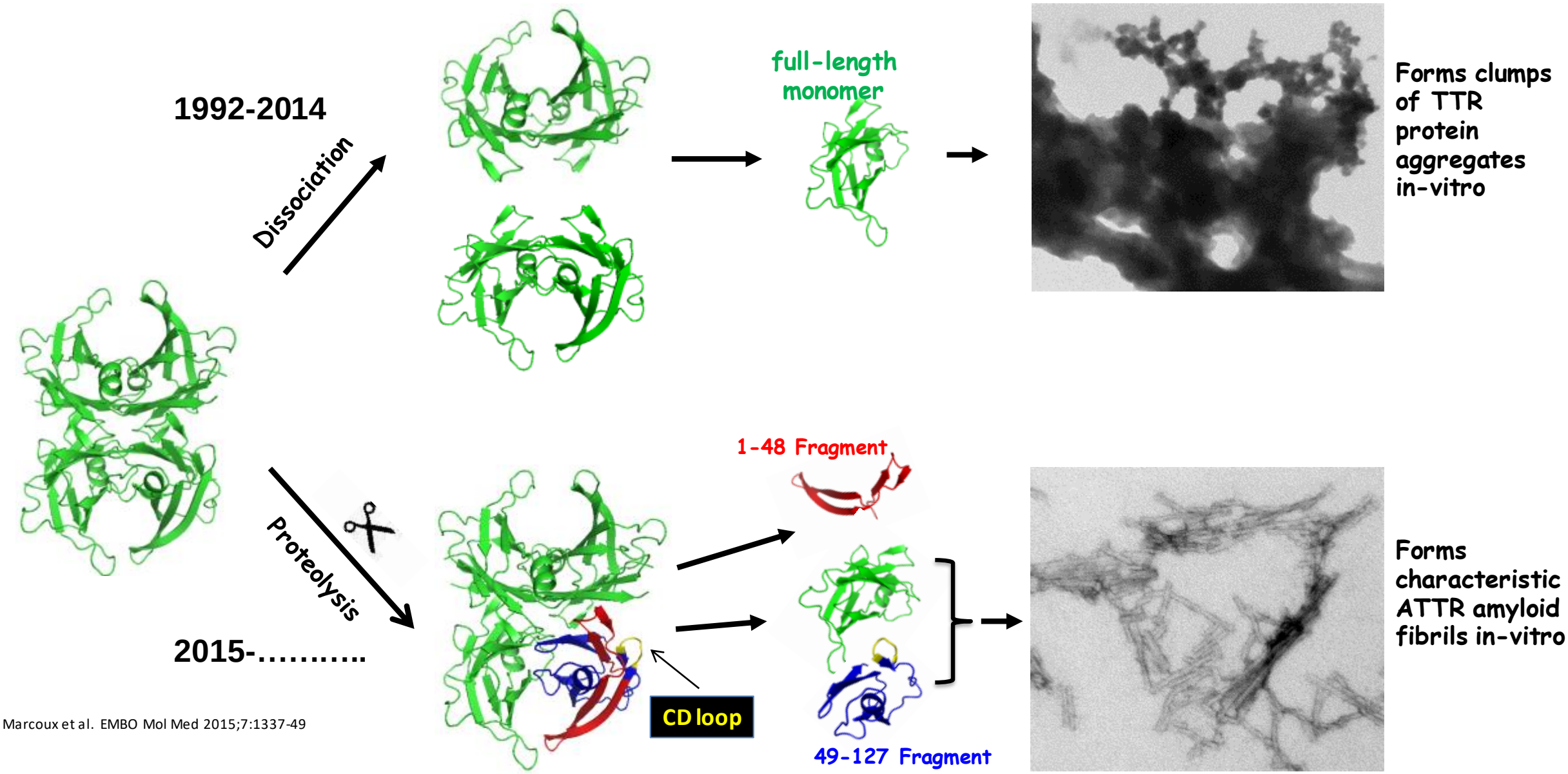
Tafamidis
Diflunisal – off label
AG10 Phase 3

Vutrisiran Phase 3
AKCEA-TTR-LRx Phase 3

Patisiran for hATTR
Inotersen for hATTR

PRX004 monoclonal antibody
Phase 1

A novel mechano-enzymatic cleavage mechanism underlies transthyretin amyloidogenesis



Marcoux et al. EMBO Mol Med 2015;7:1337-49

Stabilization versus amyloid protein knock-down

Some considerations about amyloid formation and clearance and why knock-down appeals

Stabilizers - Tafamidis, Diflunisal, AG10

- Terminology - stabilization refers to PD effect in vitro; reduced dissociation of TTR tetramers
- Predominantly occupy just one of two TTR binding pockets
  - does not prevent proteolytic cleavage of TTR tetramer
- Amount by which ATTR amyloid formation may be inhibited in-vivo is neither known nor measurable

Principle of knock-down established in AA and AL amyloidosis

- Reduction of AA and AL precursor proteins by >80% associated with regression of amyloid
- Confirmed by SAP scintigraphy and CMR; associated improvement in organ function
- Natural clearance of amyloid is slow - months to years

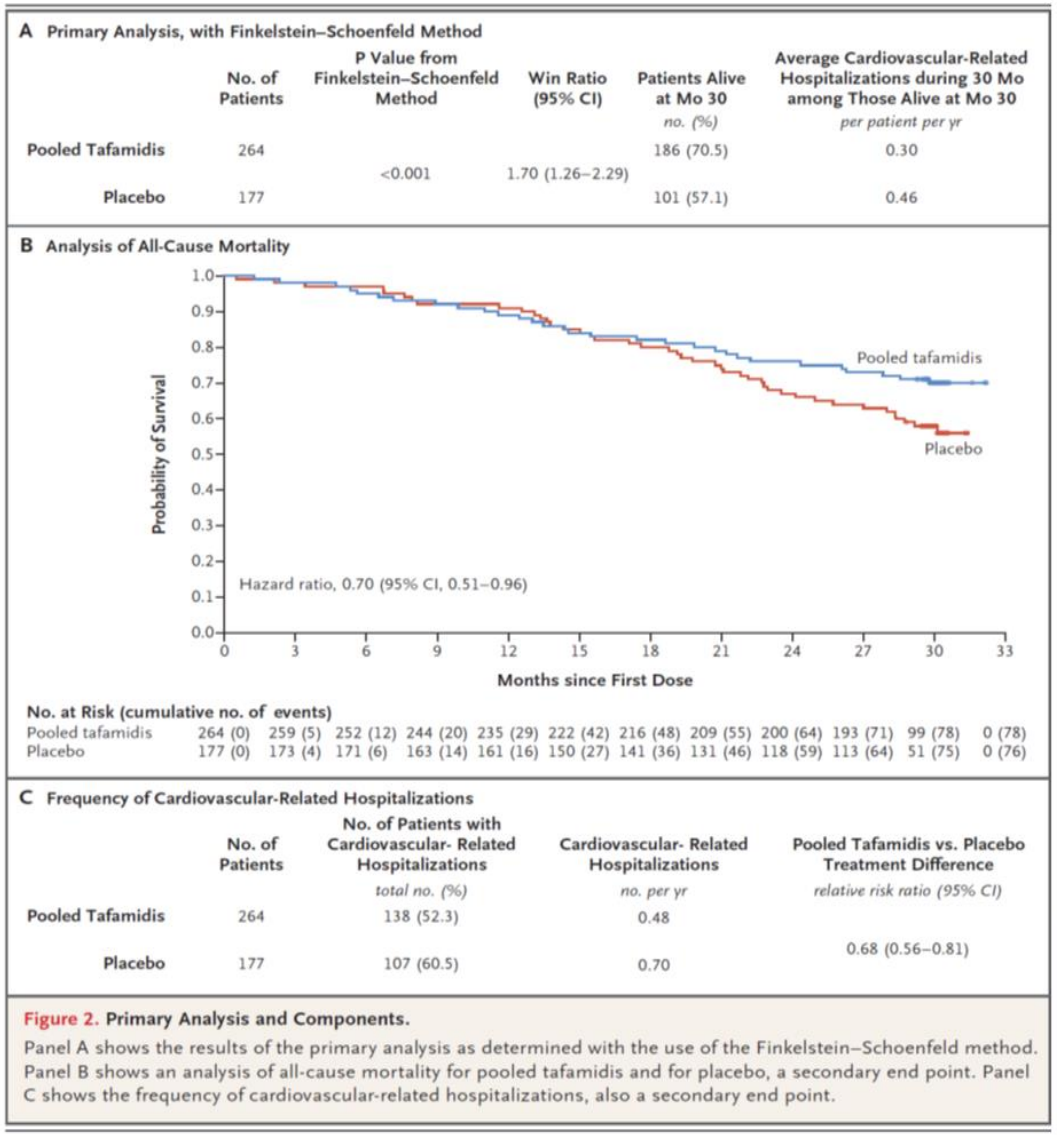
Potential for recovery of organ function

- Depends on substantial reduction in ongoing amyloid formation, enabling regression
- Requires initiation of effective treatment before organ damage is irreversible

Knock-down therapy in ATTR

- Compelling rationale
- Measurement of plasma TTR concentration provides a robust biomarker of PD response

TAFAMIDIS ATTR-ACT study results



A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30 no. (%)	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 per patient per yr
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality

No. at Risk (cumulative no. of events)

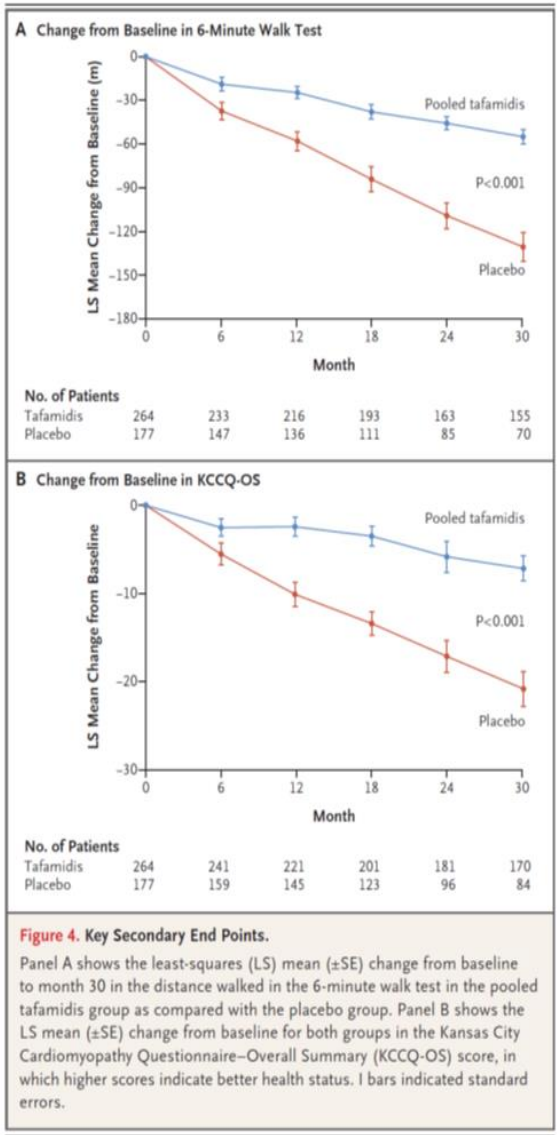
Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations total no. (%)	Cardiovascular- Related Hospitalizations no. per yr	Pooled Tafamidis vs. Placebo Treatment Difference relative risk ratio (95% CI)
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

Figure 2. Primary Analysis and Components.

Panel A shows the results of the primary analysis as determined with the use of the Finkelstein–Schoenfeld method. Panel B shows an analysis of all-cause mortality for pooled tafamidis and for placebo, a secondary end point. Panel C shows the frequency of cardiovascular-related hospitalizations, also a secondary end point.



A Change from Baseline in 6-Minute Walk Test

No. of Patients

Tafamidis	264	233	216	193	163	155
Placebo	177	147	136	111	85	70

B Change from Baseline in KCCQ-OS

No. of Patients

Tafamidis	264	241	221	201	181	170
Placebo	177	159	145	123	96	84

Figure 4. Key Secondary End Points.

Panel A shows the least-squares (LS) mean (±SE) change from baseline to month 30 in the distance walked in the 6-minute walk test in the pooled tafamidis group as compared with the placebo group. Panel B shows the LS mean (±SE) change from baseline for both groups in the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score, in which higher scores indicate better health status. I bars indicated standard errors.

Reduction in mortality and morbidity with tafamidis vs placebo but only among patients with NYHA class I/II symptoms

NT-proBNP, KCCQ score and 6 min walk distance worsened in both groups

Tafamidis associated with disease progression

Maurer MS *et al,* N Engl J Med 2018;379(11):1007–1016

INOTERSEN NEURO-TTR

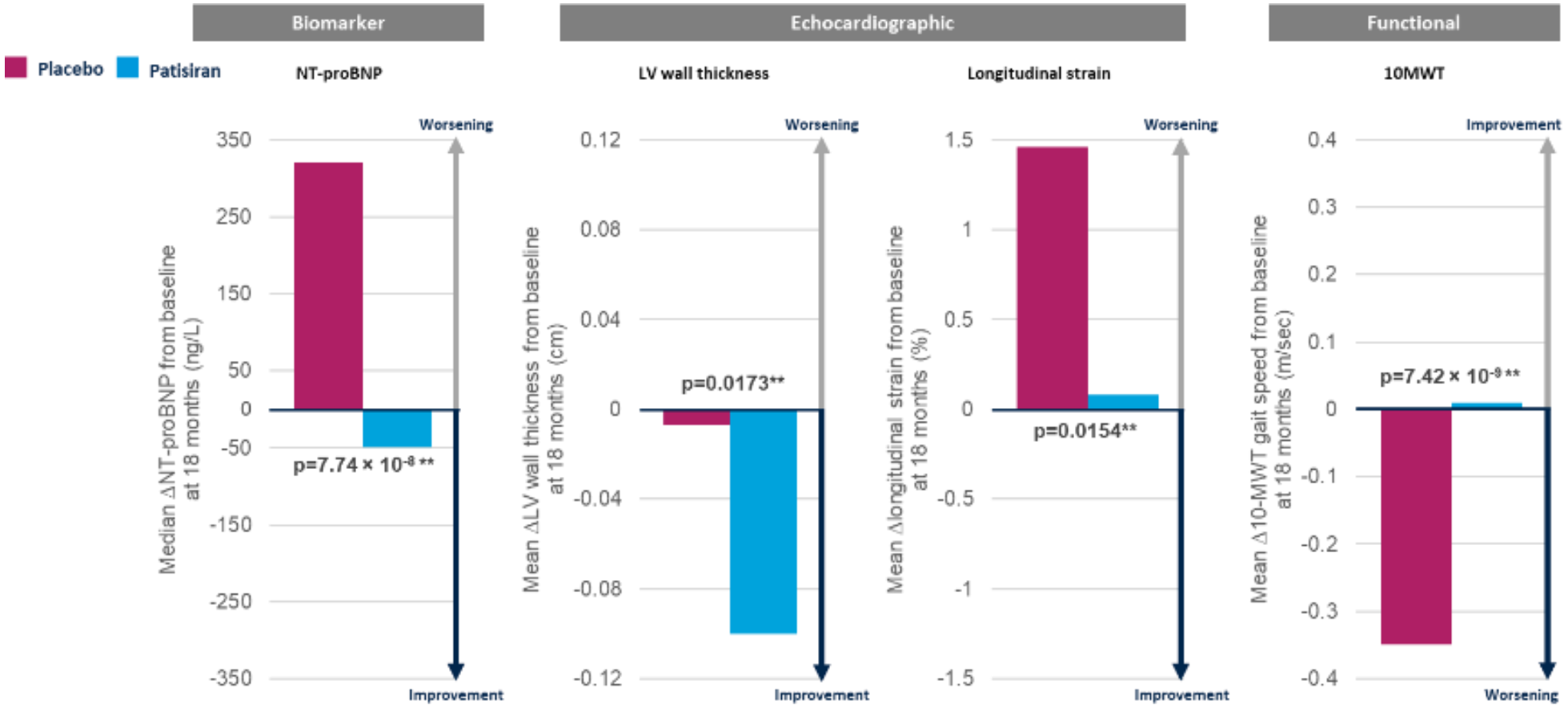
No cardiac benefit identified in sub-population of patients with hATTR amyloidosis and cardiomyopathy

	NEURO-TTR: Change from baseline		Least-square mean difference	P value
	Placebo (n=33)	Inotersen (n=75)		
Posterior wall thickness, cm	0.001 (–0.088, 0.091)	−0.025 (−0.094, 0.044)	−0.026 (−0.132, 0.0800)	**0.621**
IV septal thickness, cm	0.015 (−0.072, 0.101)	−0.042 (−0.110, 0.025)	0.057 (−0.159, 0.045)	**0.270**
Global longitudinal strain, %	0.94 (–0.23, 2.11)	1.14 (0.15, 2.13)	0.20 (−1.17, 1.56)	**0.771**

Benson MD et al. N Engl J Med 2018;379:22–31 Supplement.

PATISIRAN APOLLO cardiac subpopulation study

Cardiac benefits in cardiomyopathy sub-population - biomarker, echo and function

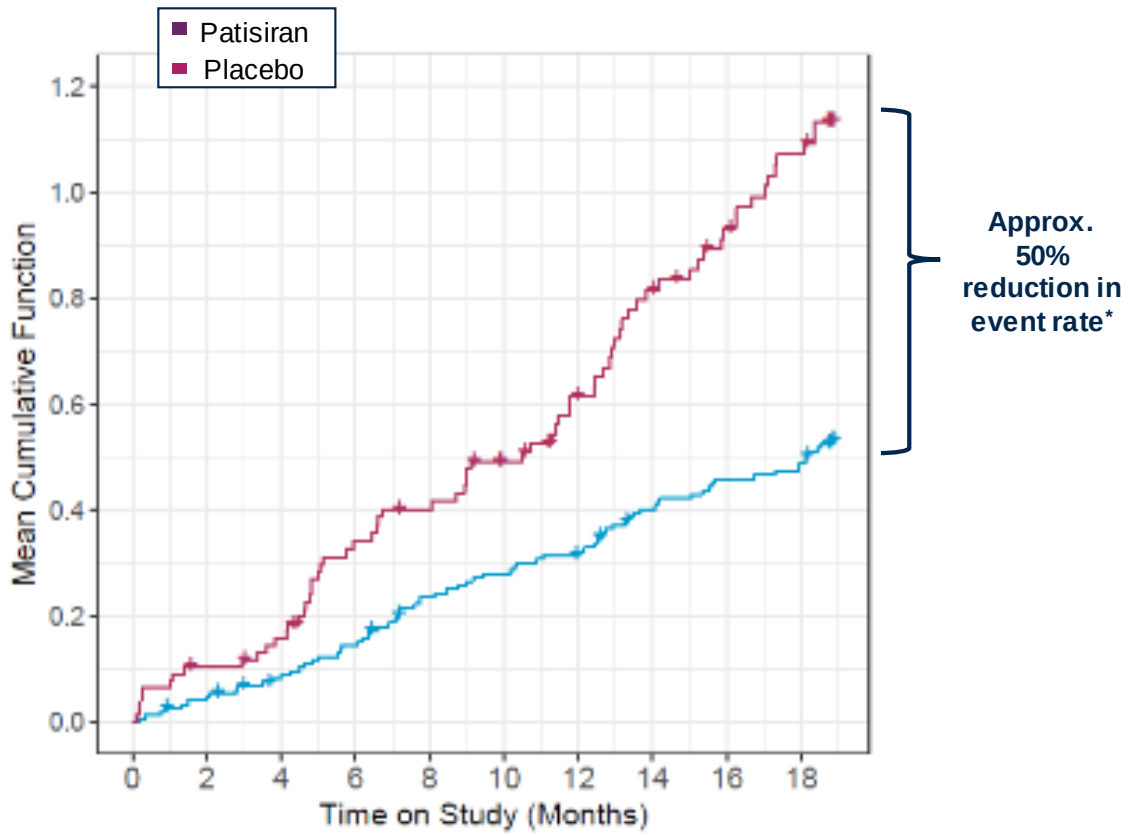


Solomon *et al*, Circulation 2019;139:431–43
Adams D *et al*, Presented at American Academy of Neurology 2018; April 2018, LA, USA

APOLLO cardiac subpopulation study cont'd

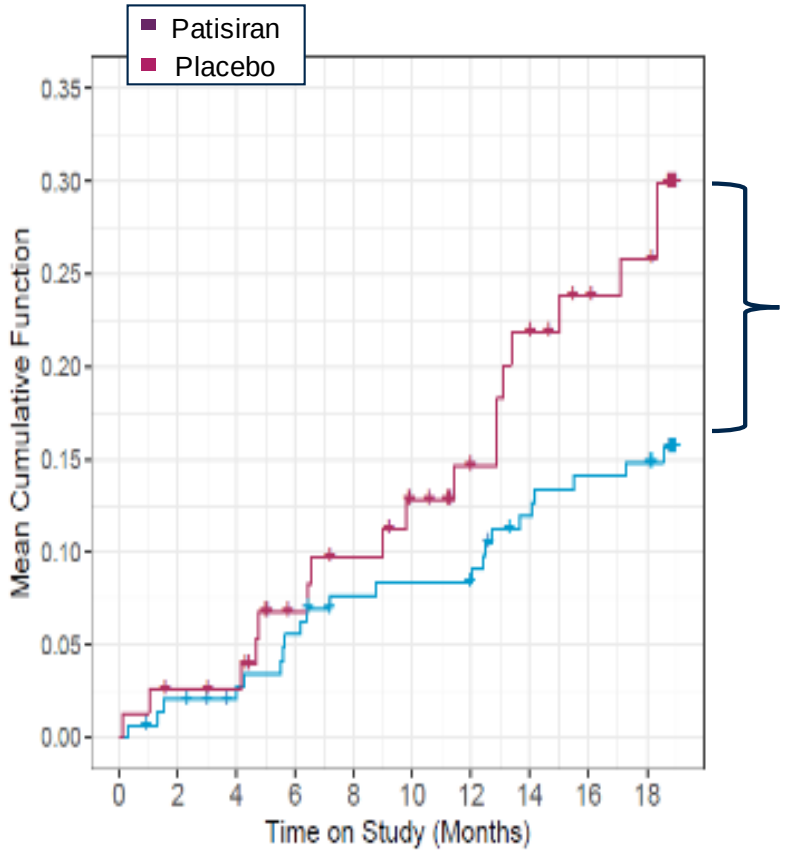
Patisiran halved the composite rate of hospitalizations and deaths in hATTR amyloidosis (post-hoc)

Composite Rate of All-Cause Hospitalization and Mortality



Approx. 50% reduction in event rate*

Composite Rate of Cardiac Hospitalization and All-Cause Mortality



Approx. 45% reduction in event rate†

Solomon *et al*, Circulation 2019;139:431–43

Regression of cardiac ATTR amyloidosis associated with patisiran

ARTICLE IN PRESS

JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2020
© 2020 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

CLINICAL RESEARCH

Reduction in CMR Derived Extracellular Volume with Patisiran Indicates Cardiac Amyloid Regression

Marianna Fontana, MD, PhD,[a,b] Ana Martinez-Naharro, MD,[a] Liza Chacko, MD,[a] Dorota Rowczenio, PhD,[a] Janet A. Gilbertson, CSci,[a] Carol J. Whelan, MD,[a] Svetla Strehina, BASci,[a] Thirusha Lane, PhD,[a] James Moon, MD,[b,c] David F. Hutt, BAPP Sci,[a] Peter Kellman, PhD,[d] Aviva Petrie, PhD,[e] Philip N. Hawkins, MD, PhD,[a] Julian D. Gillmore, MD, PhD[a]

ABSTRACT

OBJECTIVES The purpose of this study was to determine the effect of patisiran on the cardiac amyloid load as measured by cardiac magnetic resonance and extracellular volume (ECV) mapping in cases of transthyretin cardiomyopathy (ATTR-CM).

BACKGROUND Administration of patisiran, a TTR-specific small interfering RNA (siRNA), has been shown to benefit neuropathy in patients with hereditary ATTR amyloidosis, but its effect on ATTR-CM remains uncertain.

METHODS Patisiran was administered to 16 patients with hereditary ATTR-CM who underwent assessment protocols at the UK National Amyloidosis Centre. Twelve of those patients concomitantly received diflunisal as a "TTR-stabilizing" drug. Patients underwent serial monitoring using cardiac magnetic resonance, echocardiography, cardiac biomarkers, bone scintigraphy, and 6-min walk tests (6MWTs). Findings of amyloid types and extracellular volumes were compared with those of 16 patients who were retrospectively matched based on cardiac magnetic resonance results.

RESULTS Patisiran was well tolerated. Median serum TTR knockdown among treated patients was 86% (interquartile range [IQR]: 82% to 90%). A total of 82% of cases showed >80% knockdown. Patisiran therapy was typically associated with a reduction in ECV (adjusted mean difference between groups: 6.2% [95% confidence interval [CI]: 9.5% to 3.0%]; p = 0.001) accompanied by a fall in N-terminal pro-B-type natriuretic peptide concentrations (adjusted mean difference between groups: 1,342 ng/l [95% CI: 2,364 to 322]; p = 0.012); an increase in 6MWT distances (adjusted mean differences between groups: 169 m [95% CI: 57 to 2,80]; p = 0.004) after 12 months of therapy; and a median reduction in cardiac uptake by bone scintigraphy of 19.6% (IQR: 9.8% to 27.1%).

CONCLUSIONS Reductions in ECV by cardiac magnetic resonance provided evidence for ATTR cardiac amyloid regression in a proportion of patients receiving patisiran. (J Am Coll Cardiol Img 2020;■:■–■)

ECV ↓

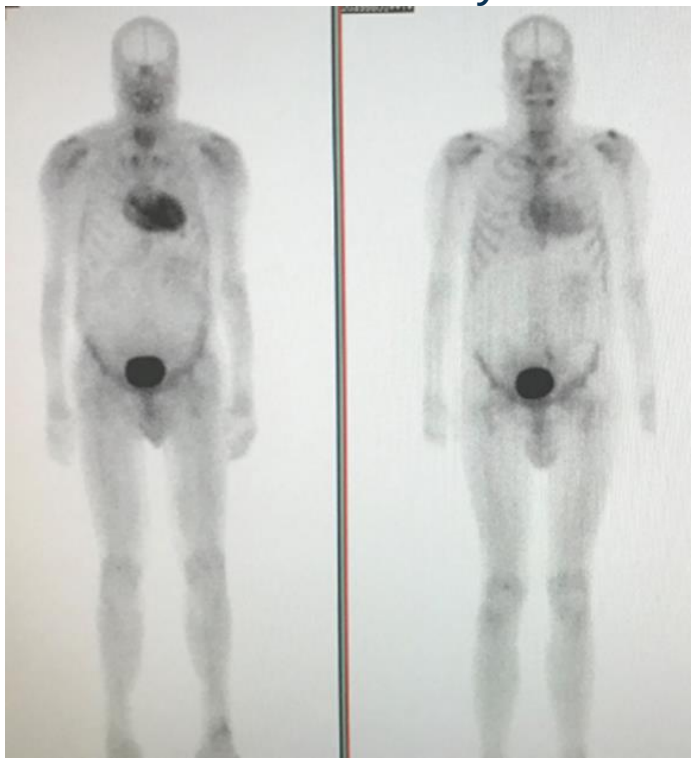
NT-proBNP ↓

6MWT ↑

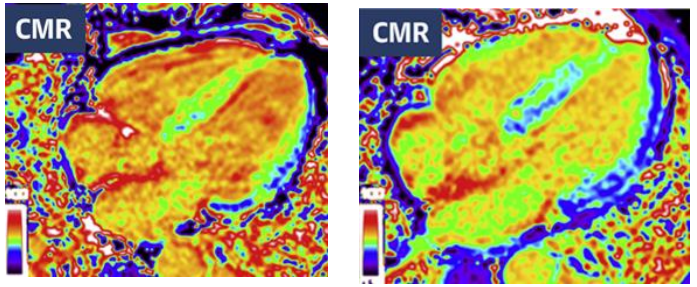
DPD Uptake ↓

Baseline + 1 year

DPD



CMR



ECV reduced by 10%

Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI: 10.1016/j.jcmg.2020.07.043

Personal Perspectives on Diagnosis, Unmet Need, and the Future

Diagnosis and Disease Understanding

- Currently, diagnosis is made late: urgency to achieve this at an earlier stage
- Highly sensitive DPD / PYP imaging method for diagnosis now widely available
  - Can identify very early cardiac amyloid
  - Potential to identify asymptomatic ATTR
  - Natural history rapidly unfolding; prior carpal tunnel and other musculoskeletal syndromes in most patients

Remaining Unmet Need Remains High in ATTR-CM

- Urgent need for treatments that halt or reverse disease
- Tafamidis does not prevent disease progression
- Eidos AG10 trial will provide much needed further insights into the stabilizer approach

Potential for Future Disease Monitoring and Treatment

- Rationale and clinical benefits of knock-down therapy firmly proven in AA and AL amyloidosis
- Cardiac MRI uniquely allows serial quantification of cardiac amyloid
  - Confirms ATTR-CM regresses following patisiran treatment in real-world setting
- Potential for combination therapies (gene silencers, stabilizers, mAbs, Crspr……)
- Potential for preventing development of heart failure with early intervention

ATTR amyloidosis 2025

Substantial awareness of this disease

Biomarkers for susceptibility and early disease identified

Amyloid histology commonly performed at carpal tunnel surgery in older people

DPD/PYP scintigraphy used routinely to exclude ATTR-CM in at-risk populations

Much wider use of multiparametric cardiac MRI

Pre-symptomatic diagnosis and treatment in many patients

Effective patient-friendly treatment that reverses the cardiomyopathy

VOICES OF **PATIENTS & CAREGIVERS**

“It was burning like fire, like somebody was just taking the sharpest thing you could possibly imagine and just stabbing.”

Candace, living with AHP

Alnylam® PHARMACEUTICALS

Expanding Alnylam TTR Franchise into Wild-Type ATTR Amyloidosis

John Vest, M.D.
Vice President, Clinical Research

Alnylam PHARMACEUTICALS

ATTR Amyloidosis

Rare, Progressively Debilitating, and Often Fatal Disease

Description

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

Hereditary ATTR (hATTR) Amyloidosis

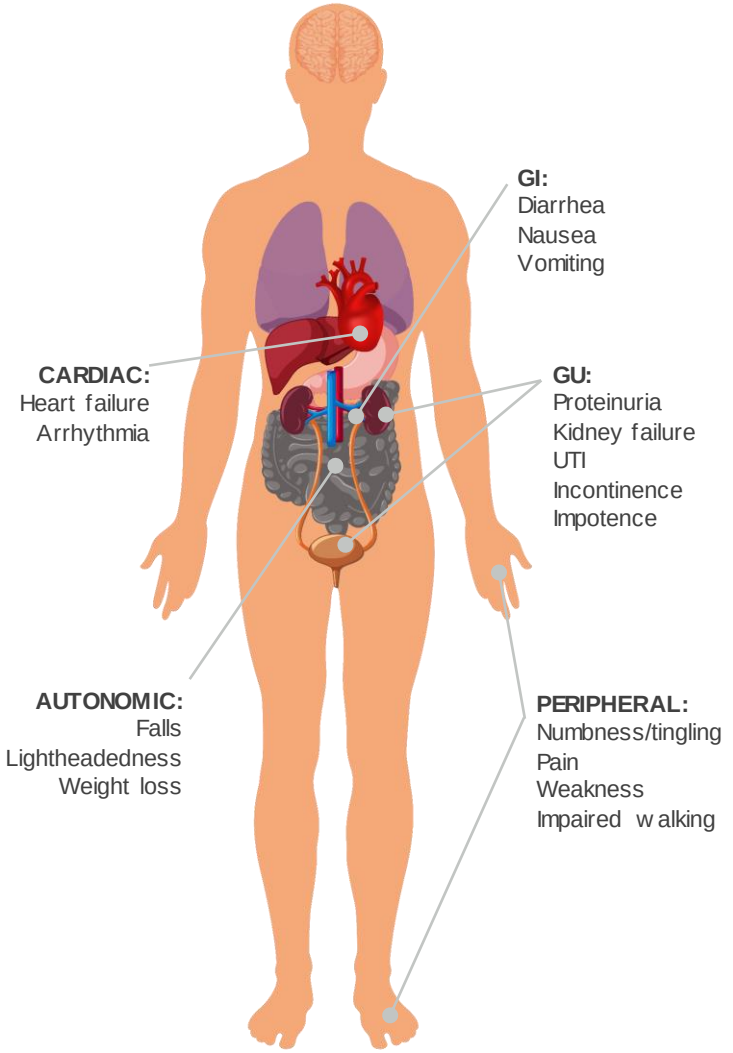
~50,000

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

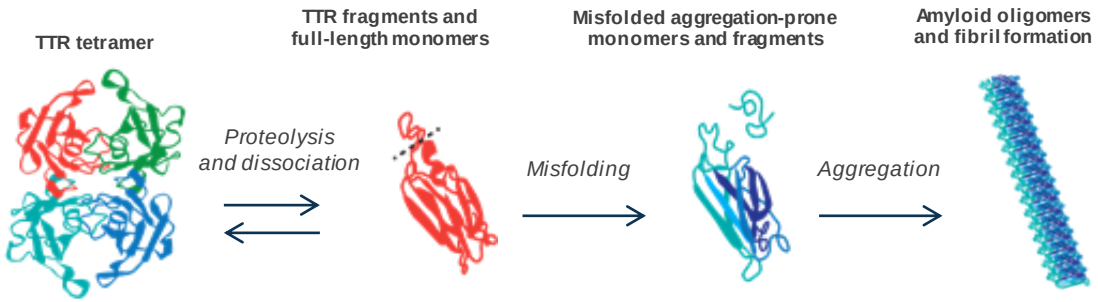
* Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012

Pathophysiology of wtATTR Amyloidosis Similar to hATTR Amyloidosis

Potentially Under-Recognized Cause of Heart Failure

wtATTR amyloidosis: non-hereditary, progressive type of ATTR amyloidosis that occurs when misfolded wt TTR accumulates as amyloid deposits in multiple organs

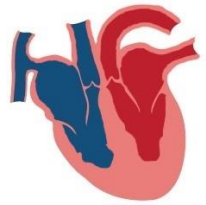
Disease Etiology



- Unclear etiology but presumed to be result of age-related mechanisms associated with TTR chemical modification and clearance
- wtATTR amyloid fibrils composed of mixture of full-length and truncated TTR (type A fibrils)
- Disease typically occurs in older individuals, and found more commonly in men

Symptoms

13% of patients aged ≥60 years with HFpEF found to have wtATTR amyoidosis[1]



- Cardiomyopathy is primary presentation of wtATTR amyloidosis; ~90% of patients report HF[2]
- Extra-cardiac manifestations also reported
  - Carpal tunnel syndrome is common initial symptom of wtATTR amyloidosis
  - Sensory, motor, and autonomic neuropathy, renal impairment, and GI symptoms have been observed

[1] Gonzalez-Lopez et al. *Eur Heart J* 2015;36:2585–94
[2] Maurer et al. *J Am Coll Cardiol* 2016;68:161–72

Dynamic Time in ATTR Amyloidosis with Cardiomyopathy

Advances in Field Drive Significant Potential as Next Generation of Treatments Progress

Deeper Understanding of Disease Etiology

- Appreciation of heart failure as a broad category
- Awareness of infiltrative cardiomyopathy
- Better understanding of ATTR amyloidosis etiology

Greater Disease Awareness and Physician Attention

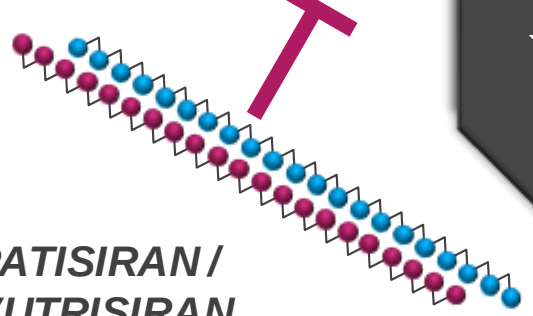
- Motivation to pursue definitive diagnosis
- Mainstream visibility and educational opportunities
- Multi-disciplinary care provided at centers of excellence

Advances and Availability of Diagnostic Tools

- Increased availability and utilization of imaging tools and genetic testing
- Technetium imaging emerging as best practice for diagnosis

RNAi Therapeutic Hypothesis in ATTR Amyloidosis

Silencing TTR Gene Expression Can Potentially Address Underlying Cause of Disease



PATISIRAN / VUTRISIRAN

siRNA sequences selected to silence both variant and wild-type TTR

Production of variant and wild-type TTR in liver*

Reduce
circulating TTR

Prevent or clear
tissue amyloid deposits

Halt or improve
progressive manifestations of disease

* >95% of TTR in circulation produced in liver

Alnylam's TTR Amyloidosis Franchise

Approved Treatment Option and Investigational Programs

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

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

About ONPATTRO

- Approved in over 30 countries
- IV administration, once every 3 weeks
- Patisiran also in clinical development as potential treatment for ATTR amyloidosis with cardiomyopathy‡

Vutrisiran

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

About Vutrisiran

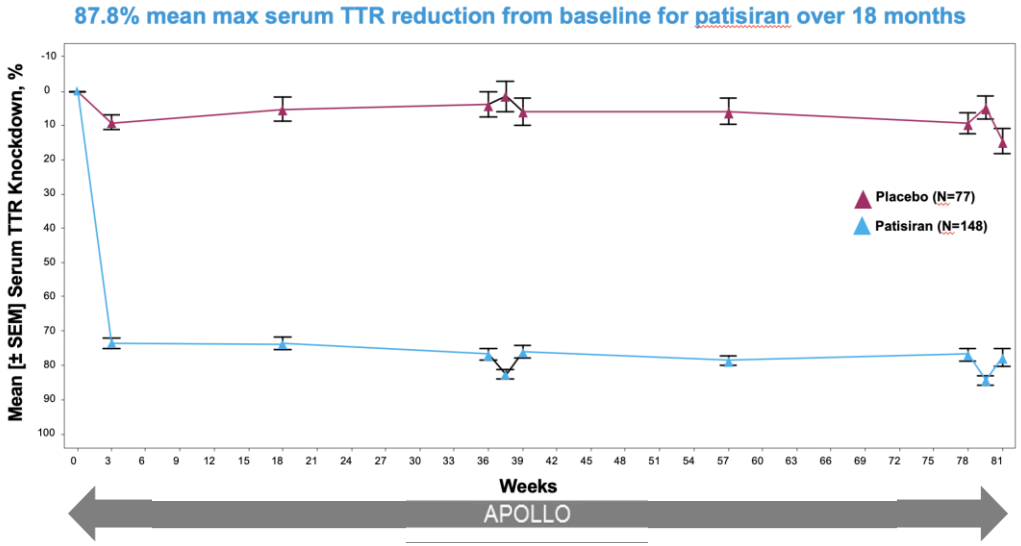
- HELIOS pivotal clinical studies ongoing
- Subcutaneous administration, once every 3 months
  - Exploring biannual dosing regimen
- Pre-filled syringe (PFS) presentation

* ONPATTRO is approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; ‡ Patisiran 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

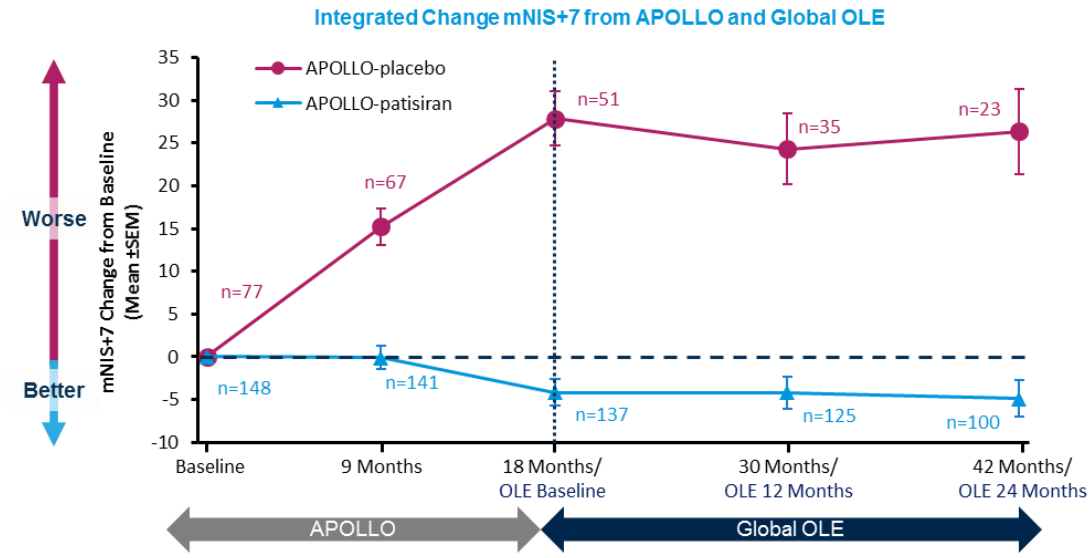
RNAi: Proven Ability to Treat Polyneuropathy of hATTR Amyloidosis

Therapeutic Hypothesis Validated by Patisiran in APOLLO and Global OLE Studies

Reduction of TTR, Disease-Causing Protein



Robust and Durable Clinical Improvement



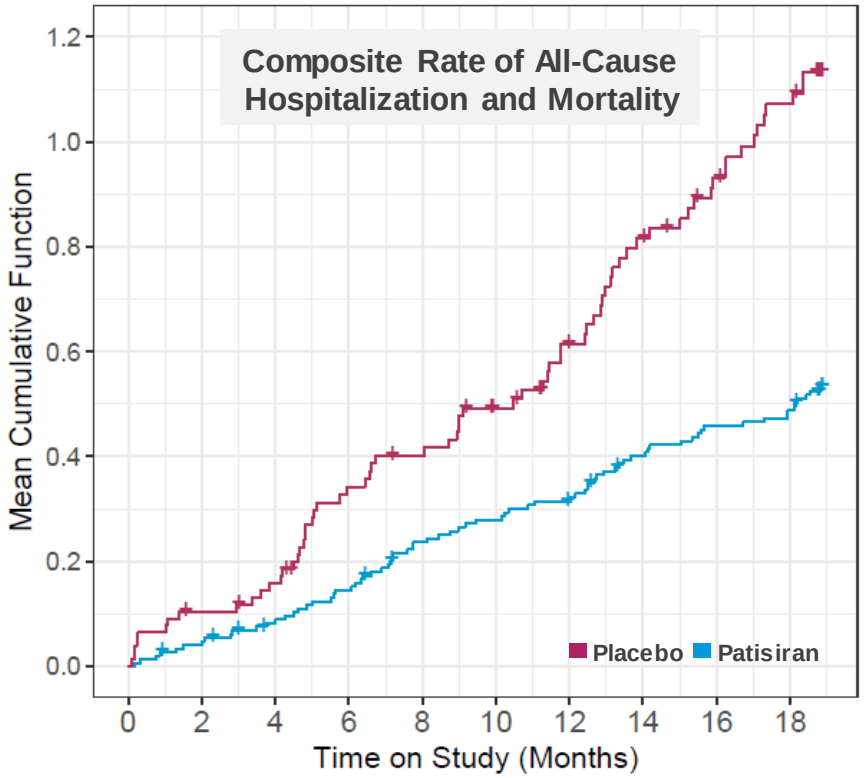
Patisiran safety profile consistent with previous studies and patisiran continues to show positive benefit:risk profile

Adams D, et al. *NEJM* 2018; Adams D, et al. *PNS Virtual Event*, 2020; Adams D, et al. *Lancet Neurology* 2020

APOLLO Phase 3 Study Results

Encouraging Evidence for Patisiran's Potential in ATTR Cardiomyopathy[1]

~50% **Reduction in all-cause hospitalization and mortality in post-hoc analysis***



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

55% • Relative reduction in **NT-proBNP** vs. placebo†
  – Effect noted as early as 9 months

0.9mm • Mean reduction in **LV wall thickness** vs. placebo‡

-1.4% • Improvement in **global longitudinal strain** vs. placebo‡

0.35m/s • Improvement in **10-MWT** vs. placebo†

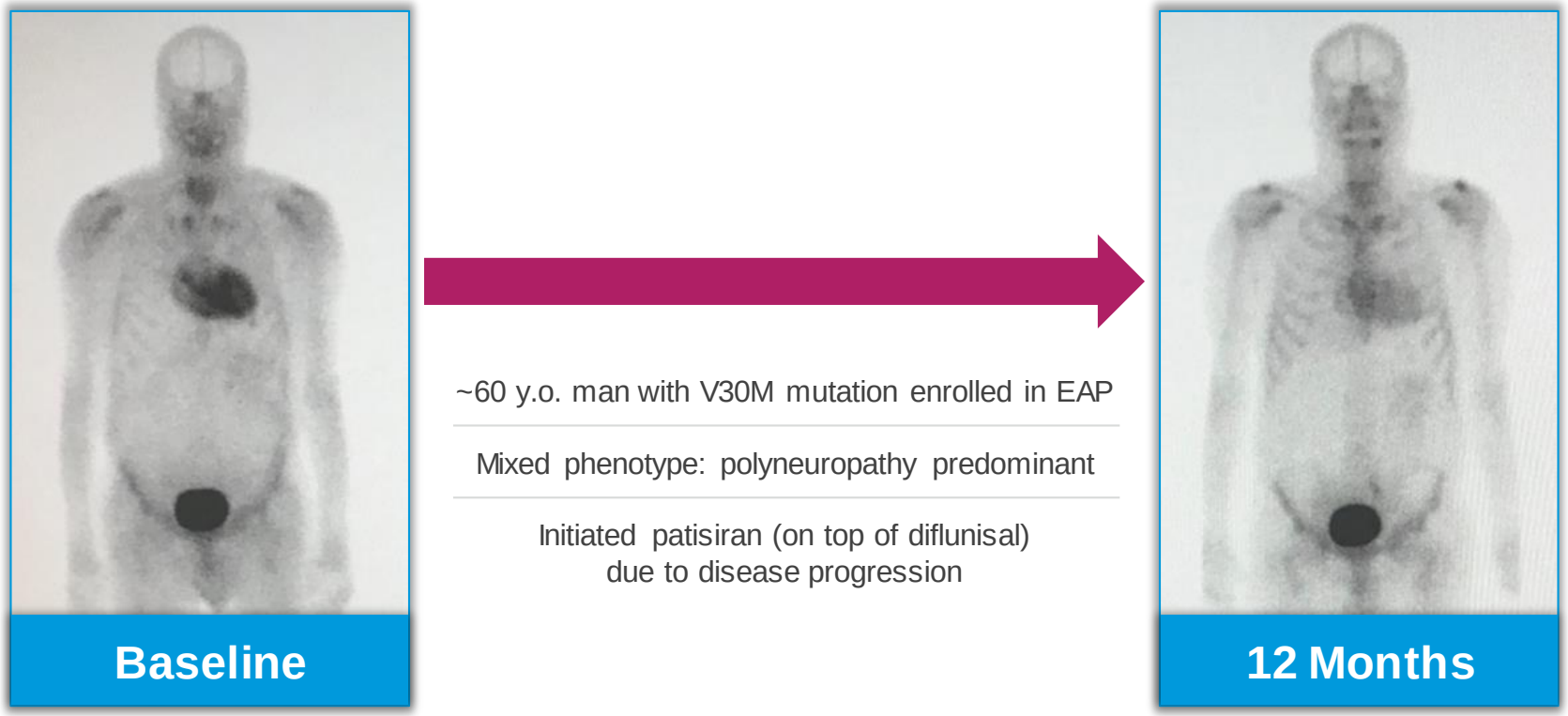
Cardiac Safety Data in Entire APOLLO Study Population:

	Placebo[2] (n=77)	Patisiran[2] (n=148)
Rates of Death/Hospitalization, per 100 py (95% CI)		
Death	6.2 (2.5 – 12.7)	3.2 (1.4 – 6.2)
All-cause hospitalization	69.7 (54.3 – 87.7)	32.9 (25.9 – 41.1)
Cardiac hospitalization	15.6 (9.0 – 24.9)	8.2 (5.0 – 12.6)
Hospitalization and/or death	71.8 (56.1 – 90.1)	34.7 (27.5 – 43.1)
Cardiac hospitalization and/or death	18.7 (11.4 – 28.8)	10.1 (6.4 – 14.9)

[1] Patisiran 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
[2] 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]
† nominal p<0.01; ‡ nominal p<0.05; Solomon S, et al. Circulation 2018

Patisiran Treatment of hATTR Amyloidosis

Initial Evidence for Potential Cardiac Amyloid Regression[1]



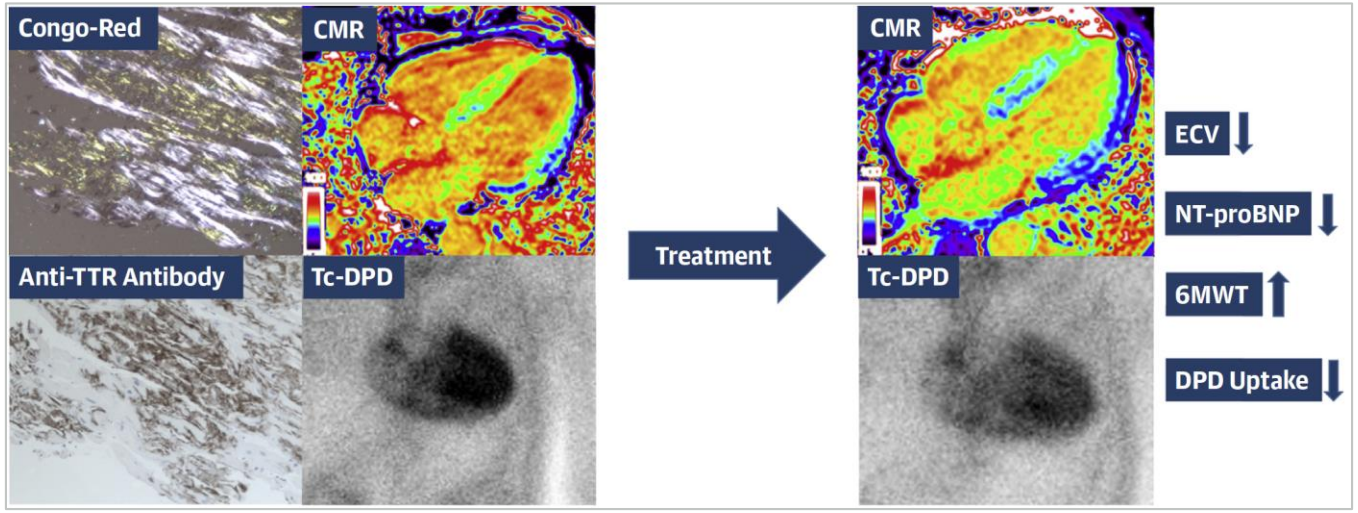
- Recent uncontrolled case series[2]
- Recently published similar findings by Nienhuis *et al*.[3]
- Patisiran treatment may be associated with cardiac remodeling and/or amyloid regression
- Cardiac effects to be further assessed in randomized, controlled trials

[1] Patisiran 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
[2] Gillmore, OTS Munich 2019
[3] Mayo Clinic Proceedings, 2019

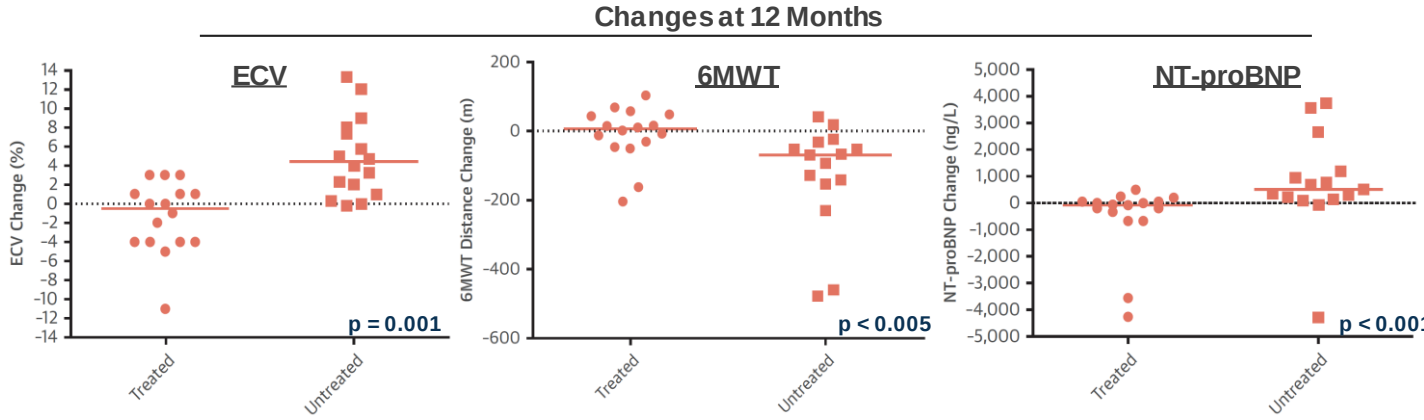
Further Evidence of Cardiac Amyloid Regression with Patisiran Treatment

Encouraging Data Recently Published[1,2]

- hATTR amyloidosis patients with cardiomyopathy
  - n=16 patisiran[3]
  - n=16 retrospectively matched control
- Reduction in cardiac amyloid burden (extracellular volume fraction; ECV) in patisiran-treated patients compared to control
- 15 of 16 patisiran-treated patients demonstrated reduction in uptake of ^{99m}Tc-DPD
  - Uptake unchanged in remaining 1 patient
- Improvement in 6-minute walk test (6-MWT) and NT-proBNP in patisiran-treated patients compared to control



Cardiac biopsies show TTR amyloid, serial planar anterior whole-body ^{99m}Tc-DPD scans, and myocardial perfusion maps showing cardiac amyloid regression in a patient receiving diflunisal and patisiran.



[1] Patisiran 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.

[2] Fontana, et al. *J Am Coll Cardiol Cardiovasc Imaging*. Oct 28, 2020. Epublished DOI: 10.1016/j.jcmg.2020.07.043

[3] Twelve (12) of 16 patisiran-treated patients received concomitant diflunisal

Largest Ever Clinical Program in ATTR Amyloidosis

Multiple Studies to Evaluate RNAi Therapeutics in Patients with ATTR Amyloidosis with Cardiomyopathy

PATISIRAN

APOLLO-B

Randomized, double-blind, placebo-controlled study of patisiran with change in 6-MWT at 12 months as primary endpoint

Enrollment completion expected
Early 2021

VUTRISIRAN

HELIOS-B

Randomized, double-blind, placebo-controlled study of vutrisiran with cardiovascular outcomes over 30 months as primary endpoint

Enrollment ongoing

Study includes optional interim analysis

HELIOS-C

*Study of vutrisiran in preventing disease manifestations **

Study Initiation Planned
Within 12-18 months

*HELIOS-C study design in development

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

Enrollment completion expected
Early 2021

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-MWT: 6-Minute Walk Test

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

1:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Primary Endpoint

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

Select Secondary Endpoints

- 6-MWT distance
- Kansas City Cardiomyopathy Questionnaire (KCCQ OS) score
- Echocardiographic parameters
- All-cause mortality and recurrent all-cause hospitalizations and HF events
- All-cause mortality
- Recurrent CV events
- NT-proBNP

ClinicalTrials.gov Identifier: NCT04153149

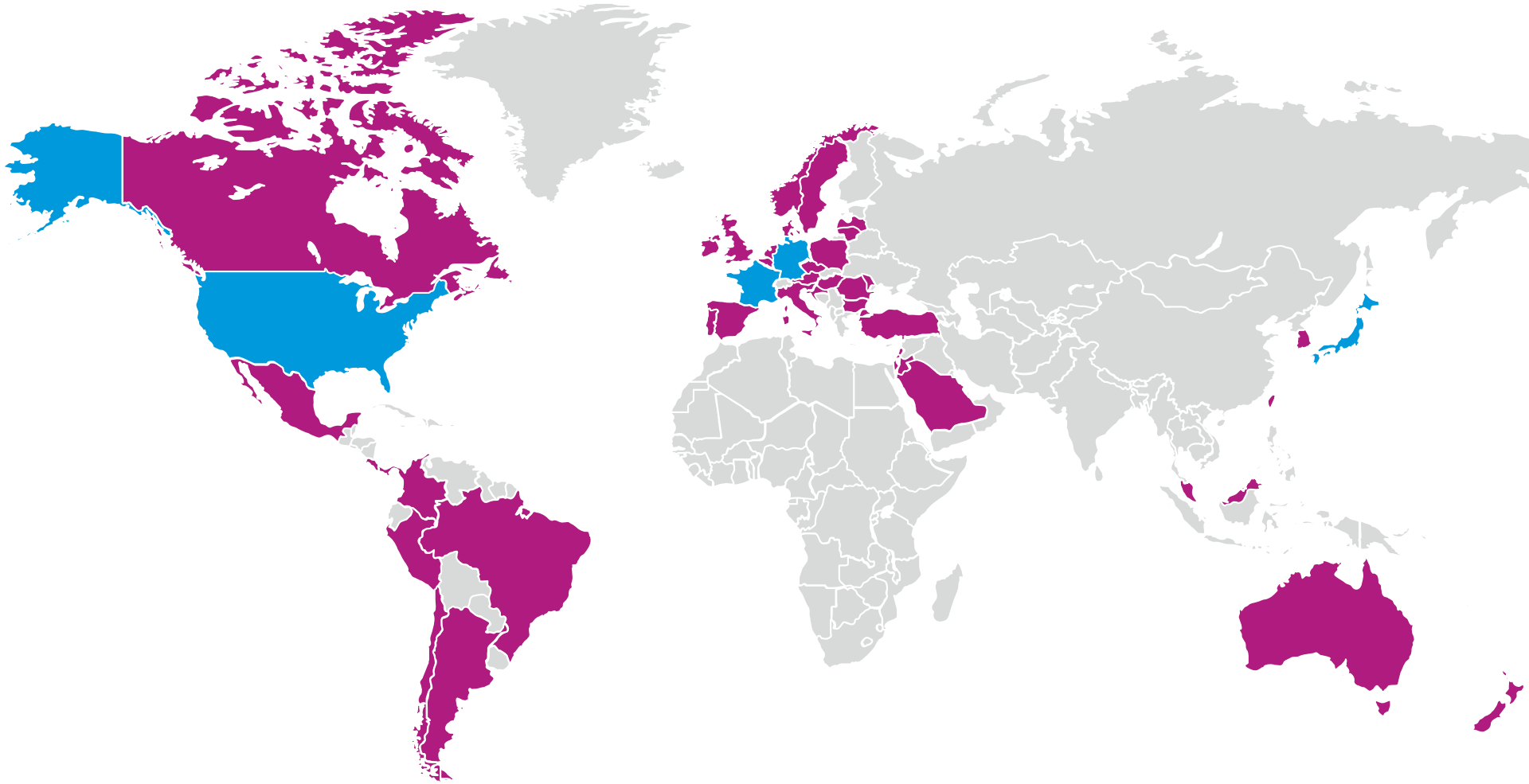
HELIOS·B

HELIOS-B Phase 3 study
Now Enrolling

Study includes optional interim analysis

APOLLO-B and HELIOS-B Utilizing Global Clinical Study Sites

Activating Sites in >40 Countries; Targeting >100 Clinical Sites



Selected for APOLLO-B and/or HELIOS-B; Tafamidis generally **available** for ATTR-CM

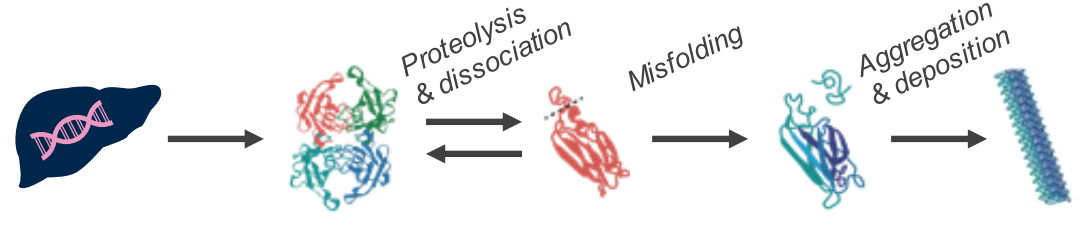
Selected for APOLLO-B and/or HELIOS-B; Tafamidis generally **unavailable** for ATTR-CM

Accelerating Enrollment

- Study footprints continue to expand
  - Opening more sites within activated countries
  - Expanding to new countries around globe
- Sites preparing for strong post-pandemic rebound
- Existing mitigations will minimize ongoing impact of COVID-19

Accumulating Evidence for RNAi Therapeutics Across ATTR Amyloidosis

Strong Foundation for APOLLO-B and HELIOS-B



POLYNEUROPATHY

CARDIOMYOPATHY

ONPATTRO

Primary endpoint
- mNIS+7

All secondary endpoints

APOLLO

VUTRISIRAN

Primary endpoint
- mNIS+7

Results expected early 2021

HELIOS·A

PATISIRAN

Post hoc analyses[1]
- Reduction in mortality and hospitalization

Exploratory endpoints
- NT-proBNP, LV thickness, 10-meter walk test

APOLLO

PATISIRAN

IIS[2]
- Clearance of cardiac amyloid, improvement in 6-minute walk test

VUTRISIRAN

Exploratory cardiac endpoints
- NT-proBNP, echo parameters, technetium imaging

Results expected late 2021

HELIOS·A

PATISIRAN

Primary endpoint
- 6-minute walk test

Results expected 2022

APOLLO·B

VUTRISIRAN

Primary endpoint
- Mortality & CV events

Enrolling

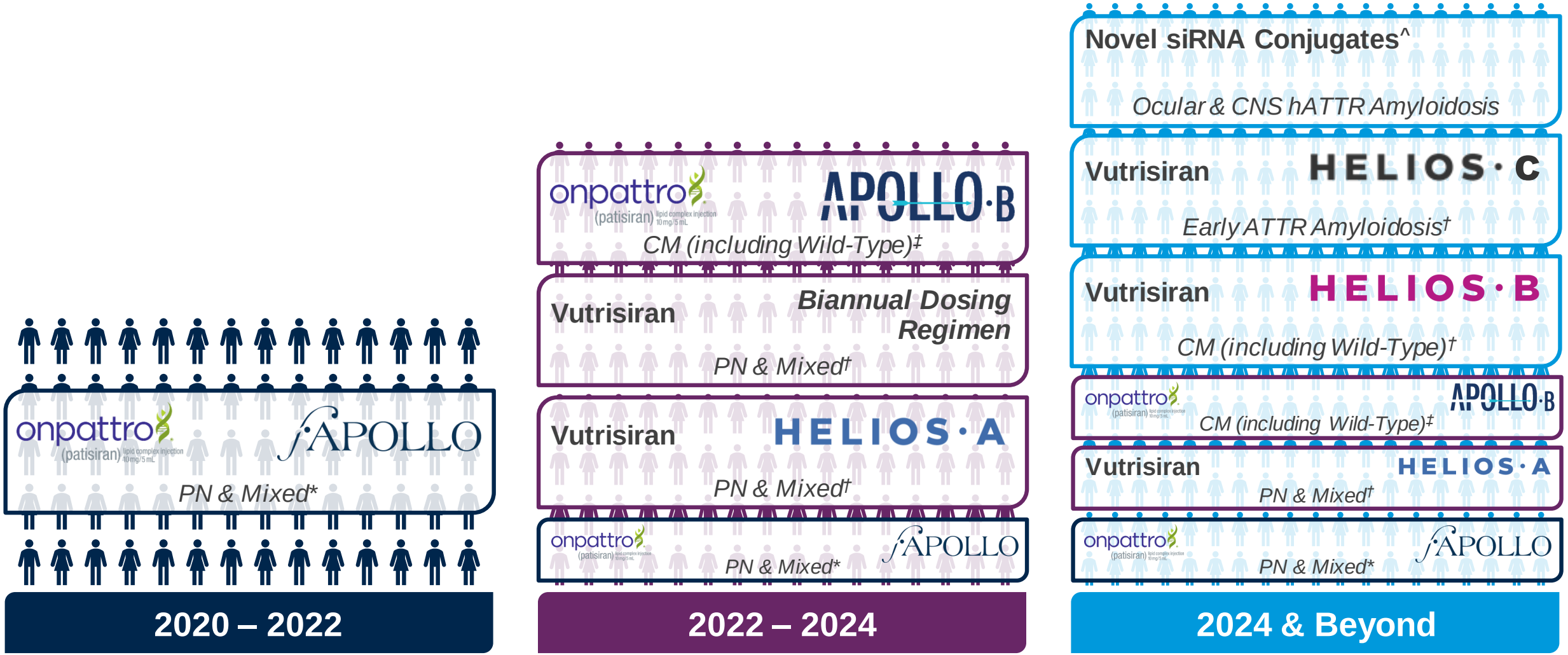
HELIOS·B

[1] Solomon S, et al. Circulation 2018

[2] Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI: 10.1016/j.jcmg.2020.07.043

Alnylam ATTR Amyloidosis Franchise

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



* ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; ‡ 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

VOICES OF **PATIENTS & CAREGIVERS**

“There have been some years where every day was a fight for life. This is a life threatening disease and I am well aware that without a cure, each of their lives will continue to be threatened by this disease time and time again. And that is a haunting thought for a mother.”

Natalie, mother of three children diagnosed with PH1

Alnylam® PHARMACEUTICALS

BRIGHAM HEALTH

BRIGHAM AND WOMEN'S HOSPITAL

Hypertension Overview

Akshay S. Desai MD, MPH
Director, Cardiomyopathy and Heart Failure Program
Cardiovascular Division
Brigham and Women's Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, MA

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Objectives

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

- Outline basic epidemiology of hypertension and continuous association between BP and CV risk
- Discuss changing definitions of hypertension and implications for treatment
- Highlight therapeutic gaps in hypertension
  - Undertreatment
  - Diurnal BP variation/Nocturnal Hypertension
  - Visit-to-Visit Variability
  - Adherence to Antihypertensive Therapy

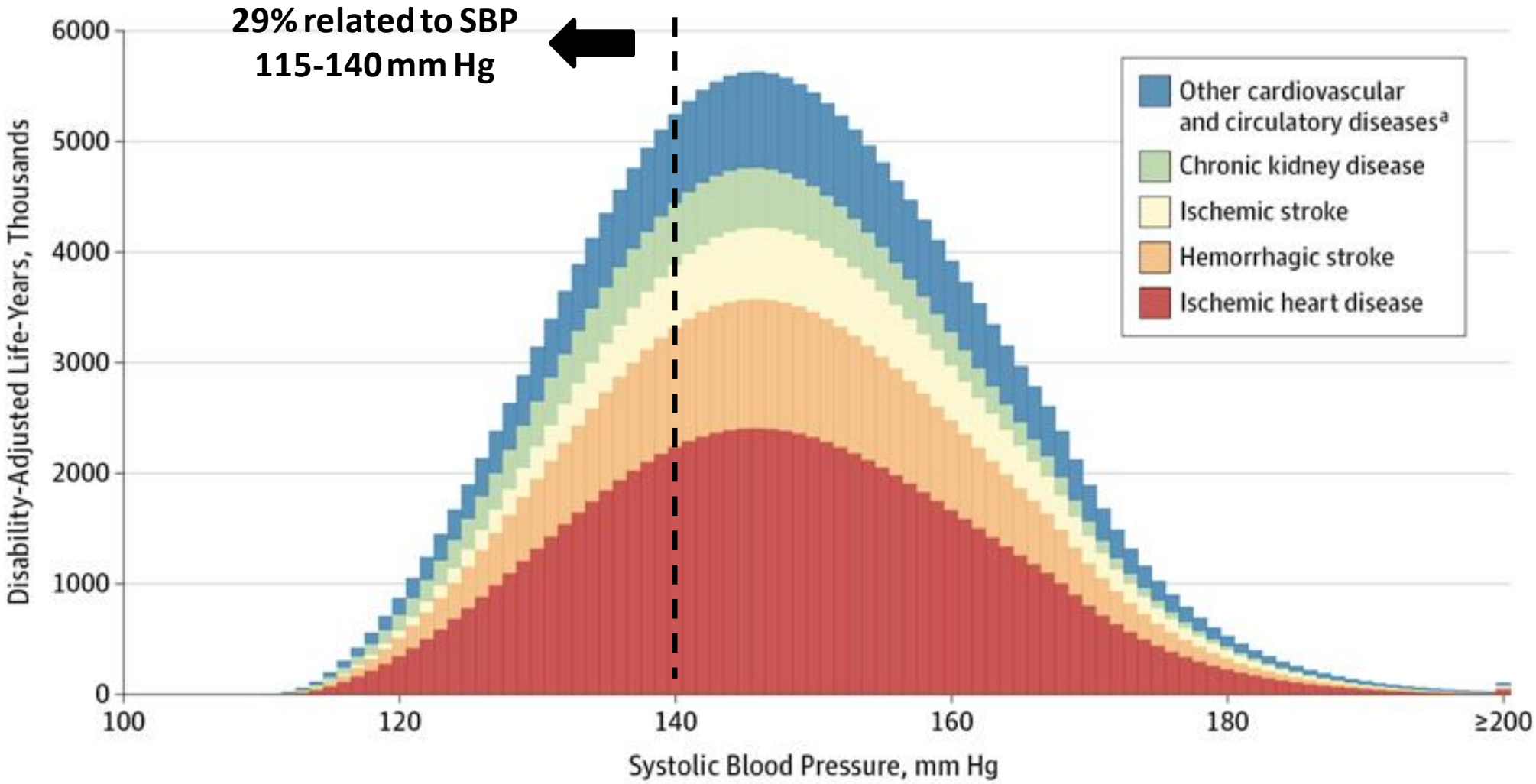
Hypertension

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

- **Leading risk factor for CVD and leading cause of DALY worldwide**
- **Suboptimal BP control is the most common attributable risk factor for CVD and cerebrovascular disease (> 50%) and leading cause of CKD progression**

Global Disability-Adjusted Life Years by SBP level and Cause

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

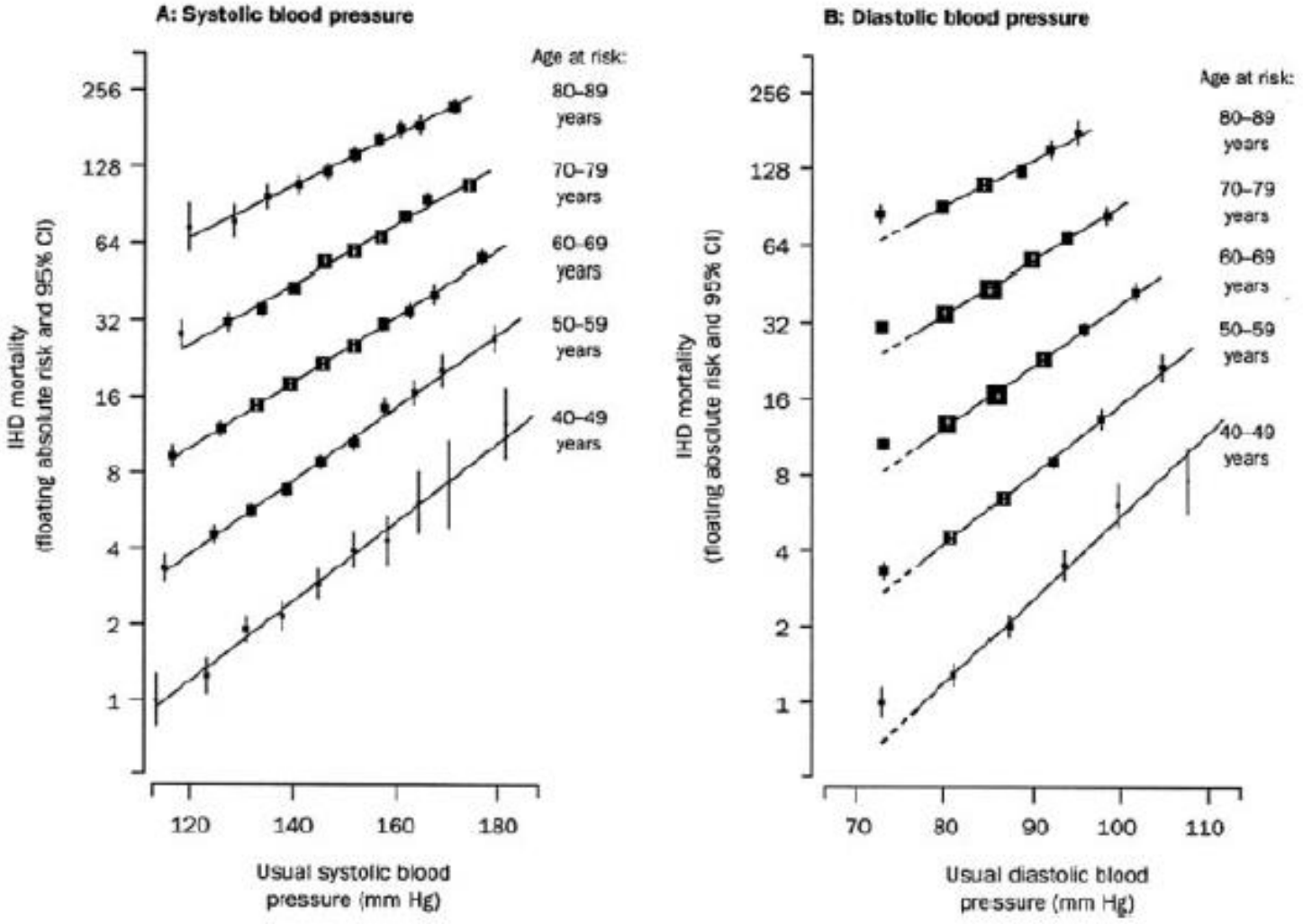


*1 DALY = 1 year of healthy life lost

Forouzanfar MH, et al. JAMA. 2017;317(2):165-182

Continuous Relationship between BP and CV risk

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

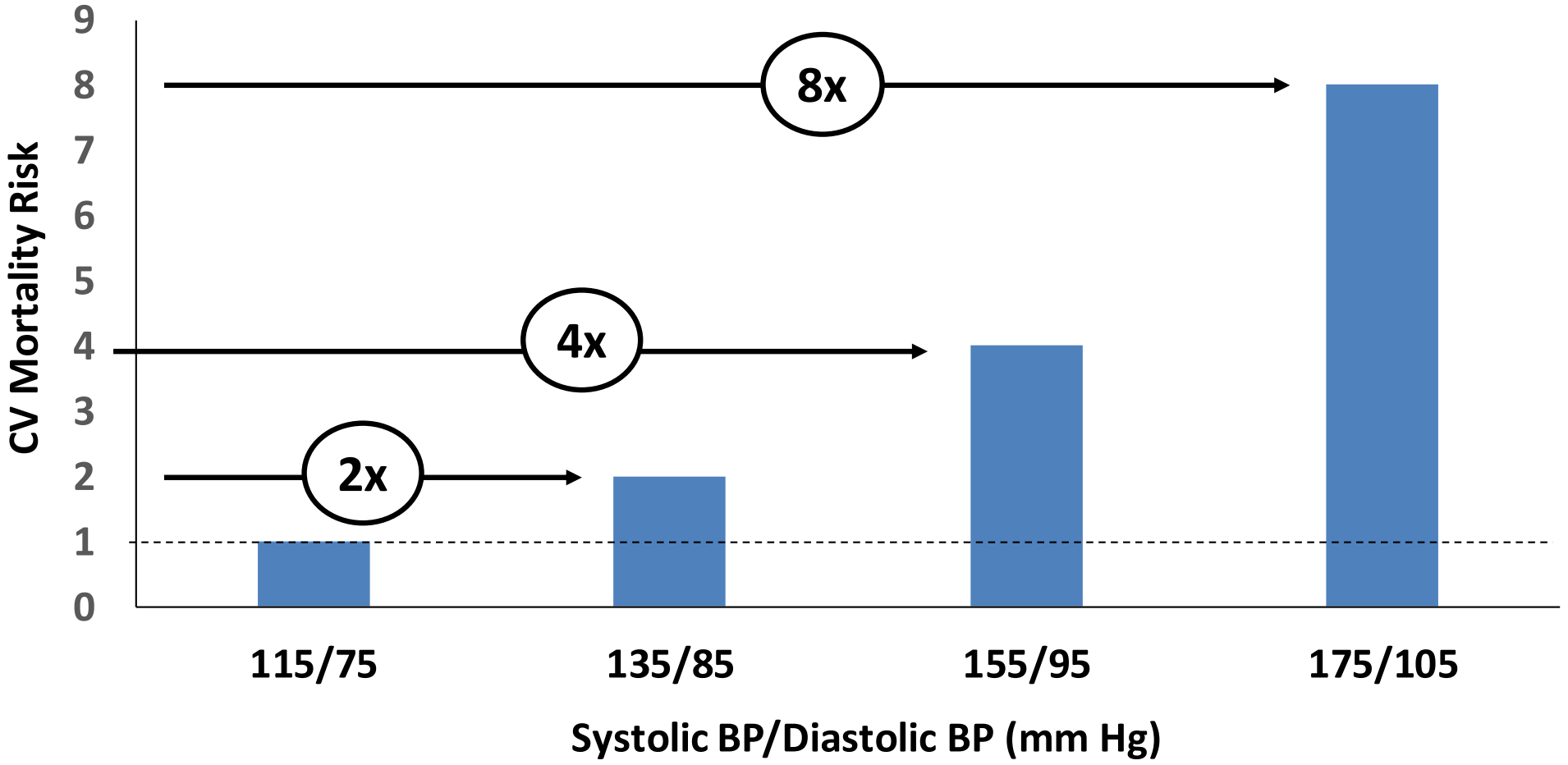


- At all ages and in both men and women, BP maintains a continuous, graded association with risk for fatal + nonfatal stroke, ischemic heart disease, heart failure
- No variation by ethnicity
- Risk persists down to a nadir of 115/75 mm Hg

Lewington S, et al. Lancet 2002;360:1903–1913
Chobanian A, et al. Hypertension. 2003;42:1206–1252

Doubling of Risk for each 20/10 mm Hg BP Increment

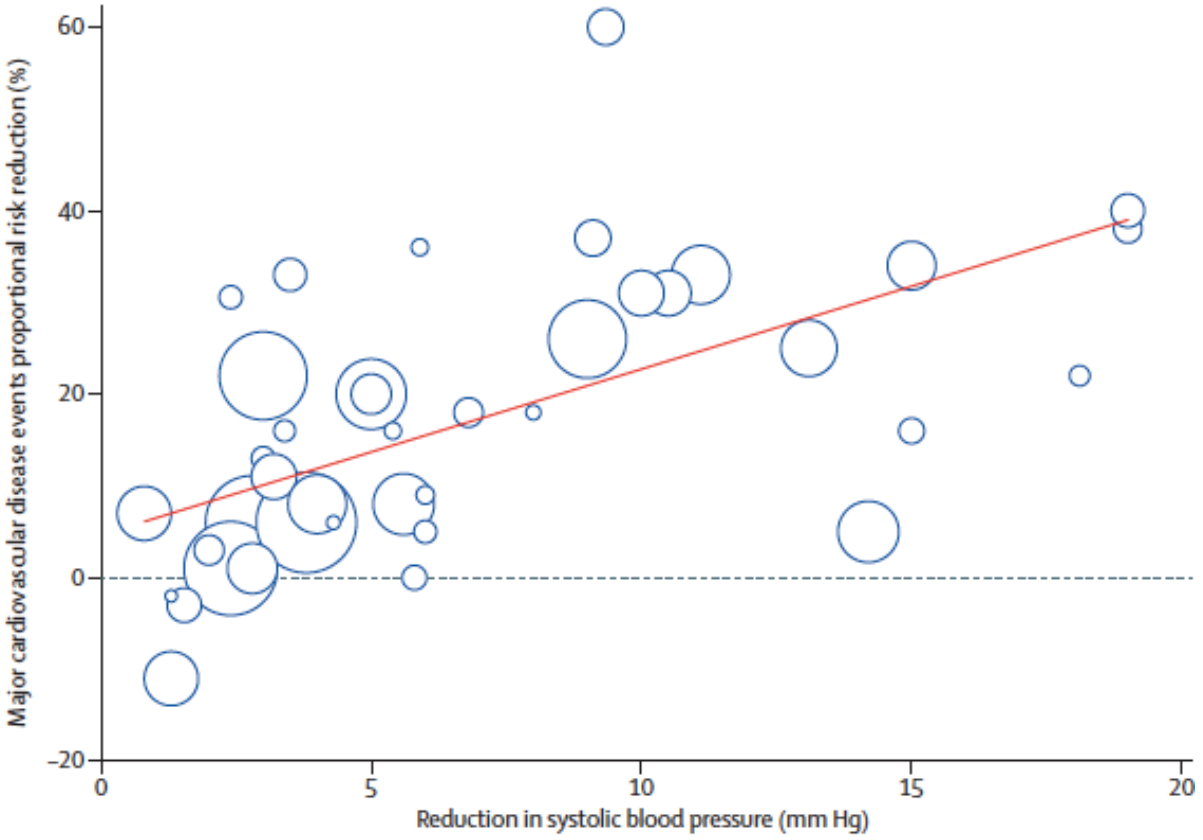
BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL



Lewington S, et al. Lancet 2002;360:1903–1913
Chobanian A, et al. Hypertension. 2003;42:1206–1252

Reduction in CV Risk with Antihypertensive Therapy

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL



Meta-analysis of 123 studies, 613815 patients

	Risk reduction per 10 mm Hg decrease in SBP
Major CV Events	**20%**
CHD	**17%**
Stroke	**27%**
HF	**28%**
Renal Failure	**5%**
All cause mortality	**13%**

- No variation in benefit by comorbidity
- Consistent benefits in trials with lower initial BP (< 130 mm Hg)
- Effects largely consistent across drug classes (but beta-blockers slightly inferior)

Ettehad D, et al. Lancet 2016; 387: 957–67

Lifestyle Modification for BP Control

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

Modification	Recommendation	Approximate SBP Reduction Range
Weight reduction	Maintain normal body weight (BMI=18.5-25)	5-20 mmHg/10 kg weight lost
DASH eating plan	Diet rich in fruits, vegetables, low fat dairy and reduced in fat	8-14 mmHg
Restrict sodium intake	<2.4 grams of sodium per day	2-8 mmHg
Physical activity	Regular aerobic exercise for at least 30 minutes at least 5 days of the week	4-10 mmHg
Moderate alcohol	≤2 drinks/day for men and ≤1 drink/day for women	2-4 mmHg

Chobanian AV et al. *JAMA* 2003;289:2560-2572

Pharmacologic Therapy of Hypertension

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

ACE Inhibitors/ **A**ngiotensin Receptor Blockers

Beta Blockers

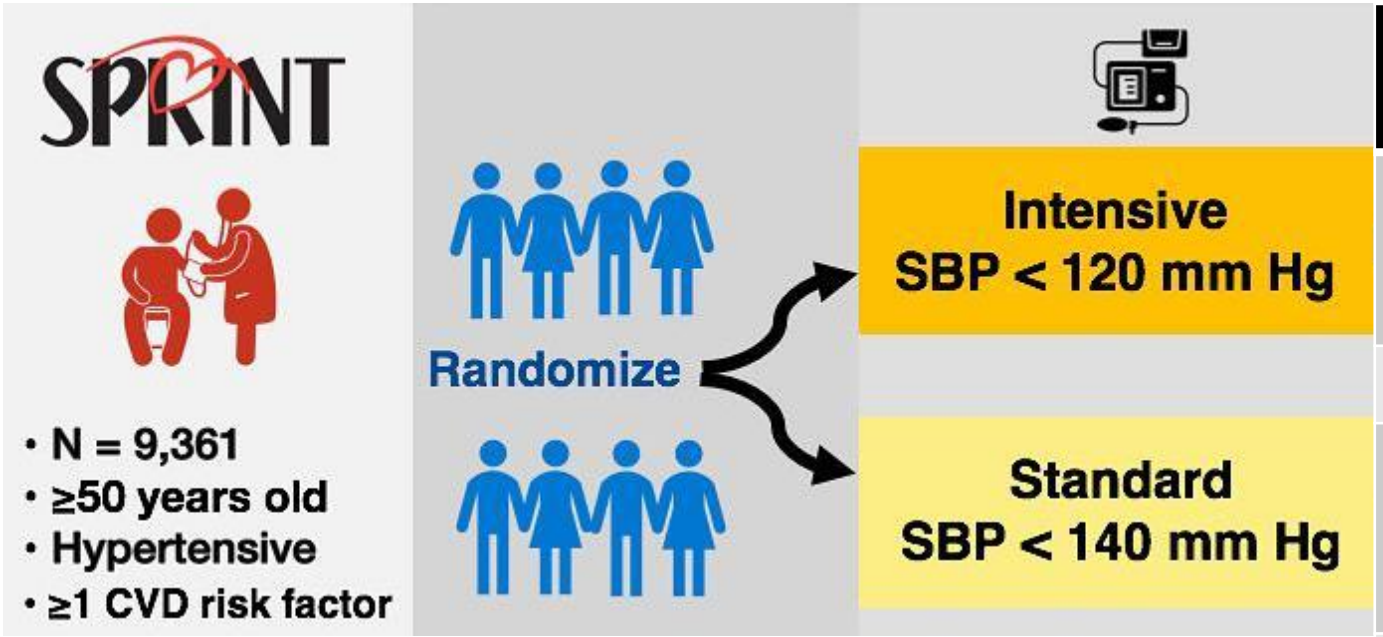
Less Effective
? Higher rates of stroke due to increase in visit-visit variability
Higher rates of Treatment Discontinuation
RESERVE FOR Established HFrEF/Prior MI

Calcium Channel Blockers

Diuretics

SPRINT: Intensive vs. Standard BP Control

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL



	EFFICACY		SAFETY	
	Primary Outcome**	Mortality	Hypotension	AKI
Intensive SBP < 120 mm Hg	5.2%	3.3%	3.4%	4.4%
Standard SBP < 140 mm Hg	6.8%	4.5%	2.0%	2.6%
	HR 0.75*	HR 0.73*	HR 1.7*	HR 1.7*

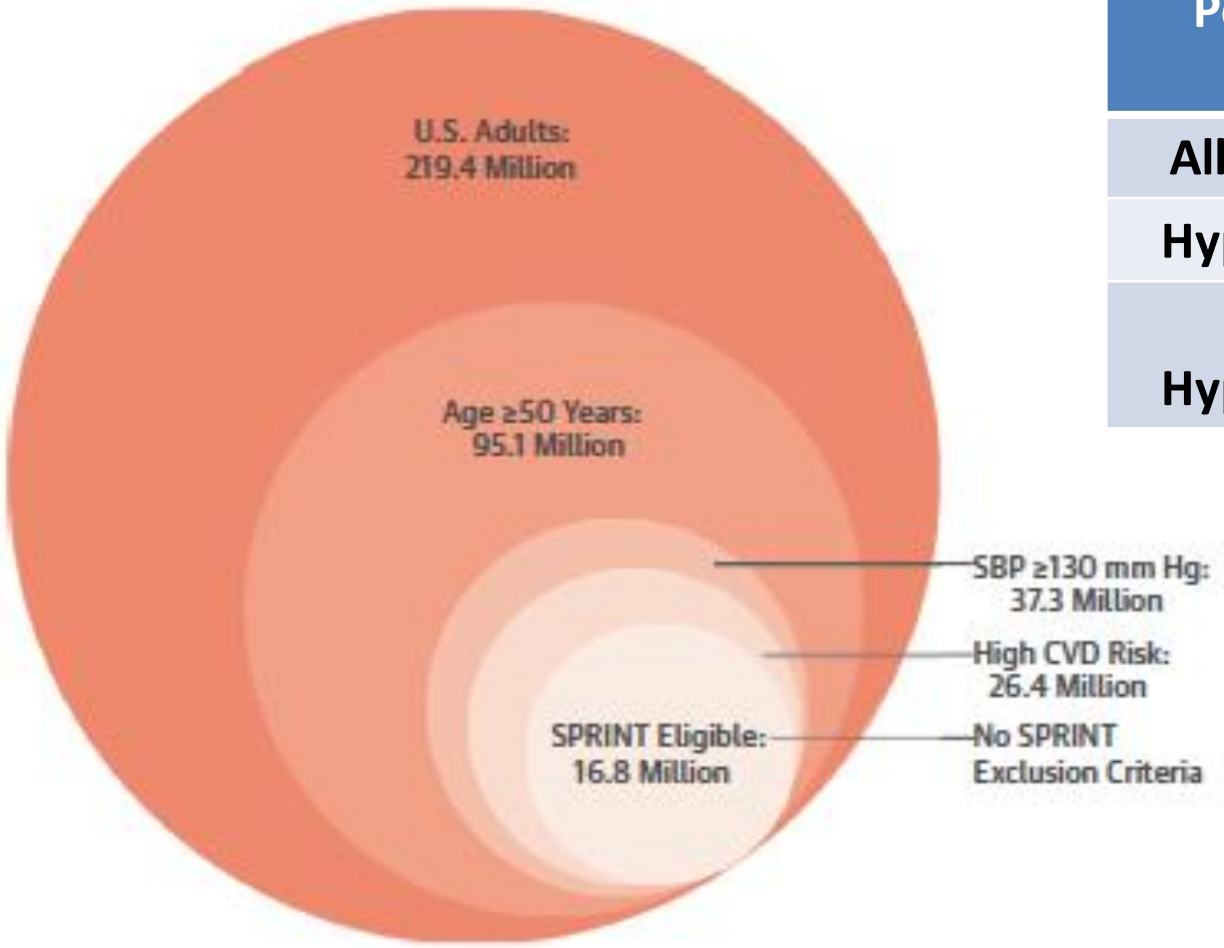
*p<0.001
**MI, ACS, Stroke, HF, or CV Death

- Terminated early for overwhelming benefit at median follow up of 3.26 yrs
- Mean SBP 122 mm Hg vs. 135 mm Hg
- Mean 2.8 vs. 1.8 antihypertensives

SPRINT Research Group. N Engl J Med 2015; 373:2103-2116

SPRINT Results: Generalizability

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL



Population	Number in millions	% SPRINT Eligible
All US Adults	219.4	7.6%
Hypertension	68.5	20%
Treated Hypertension	49.5	16.7%

Bress, A.P. et al. J Am Coll Cardiol. 2016; 67(5):463–72.

Changing BP Targets

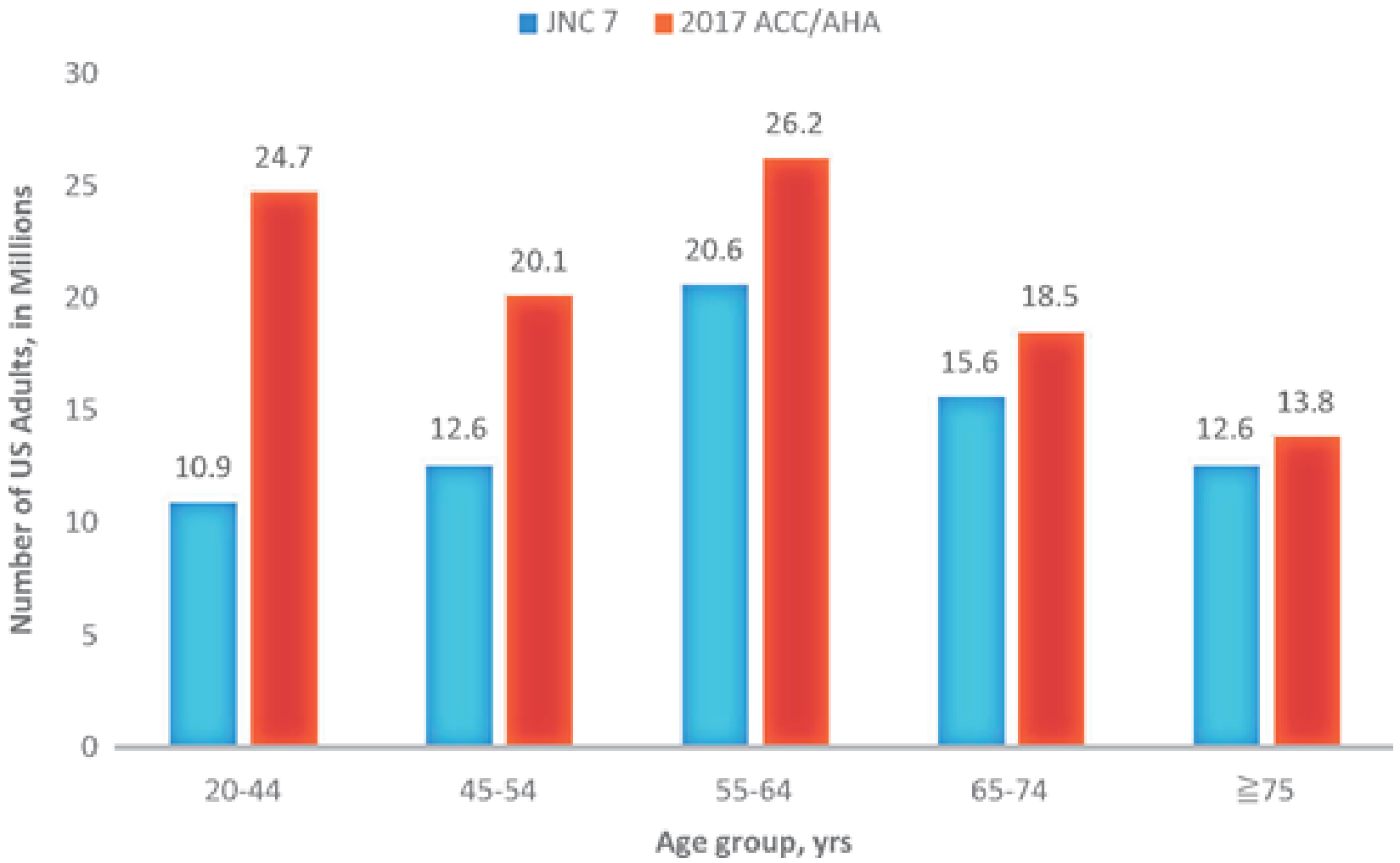
BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

SBP		DBP	2003 JNC 7	2017 ACC/AHA
<120	and	<80	Normal BP	Normal BP
120–129	and	<80	Prehypertension	Elevated BP
130–139	or	80–89	Prehypertension	Stage 1 hypertension
140–159	or	90-99	Stage 1 hypertension	Stage 2 hypertension
≥160	or	≥100	Stage 2 hypertension	Stage 2 hypertension

Whelton PK et al. J Am Coll Cardiol. 2017; doi: 10.1016/j.jacc.2017.11.006. [Epub ahead of print].

Hypertension Prevalence by New Definitions

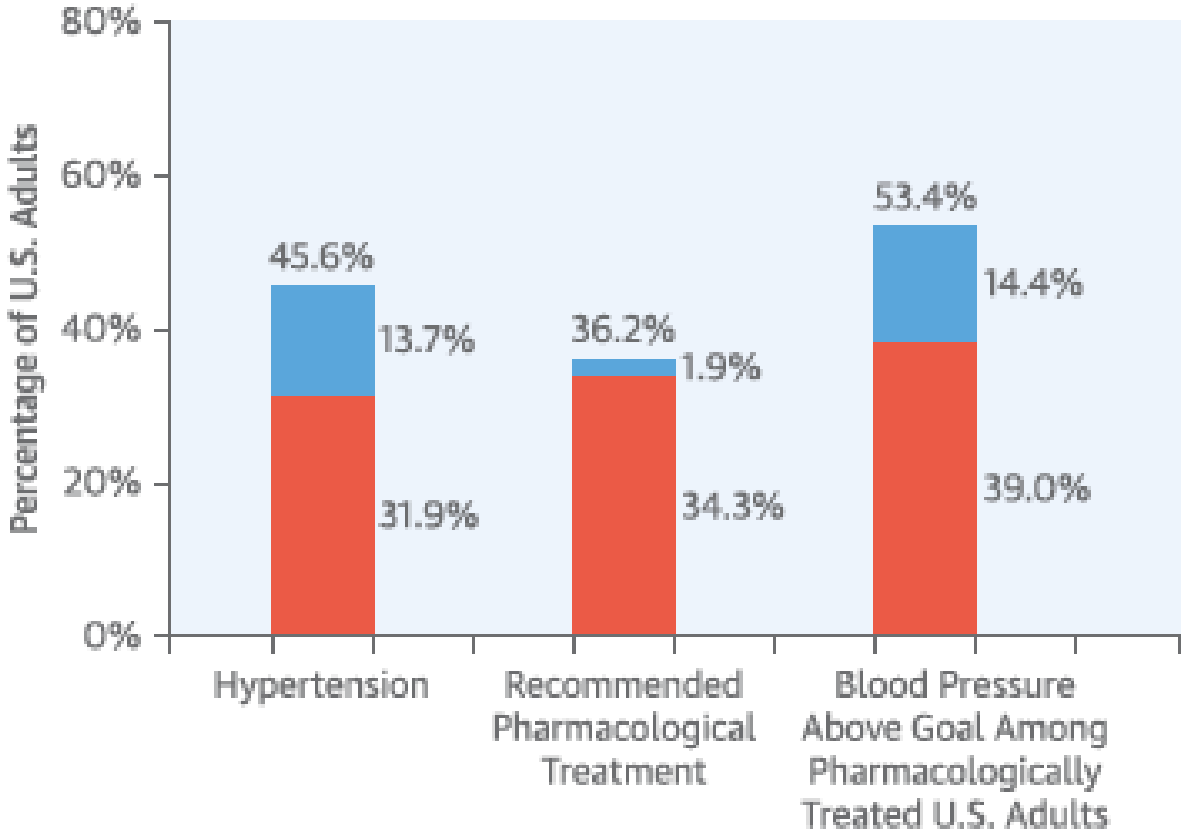
BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

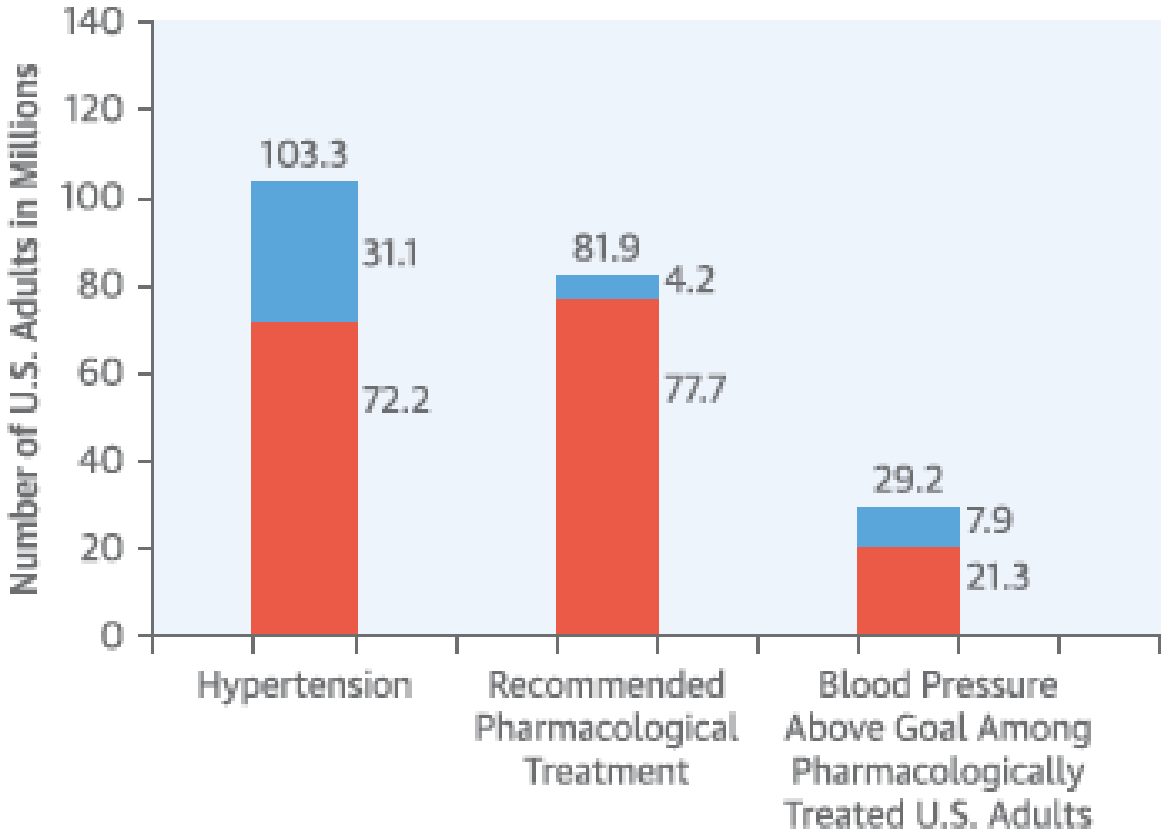


Tiwana J, Yang E. European Heart Journal, 2019; 40(26): 2106–2109

US Population Implications of New ACC/AHA BP Targets

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL





2017 ACC/AHA Guideline But Not JNC7
2017 ACC/AHA Guideline and JNC7

Muntner P, et al. Circulation. 2018;137:109–118.

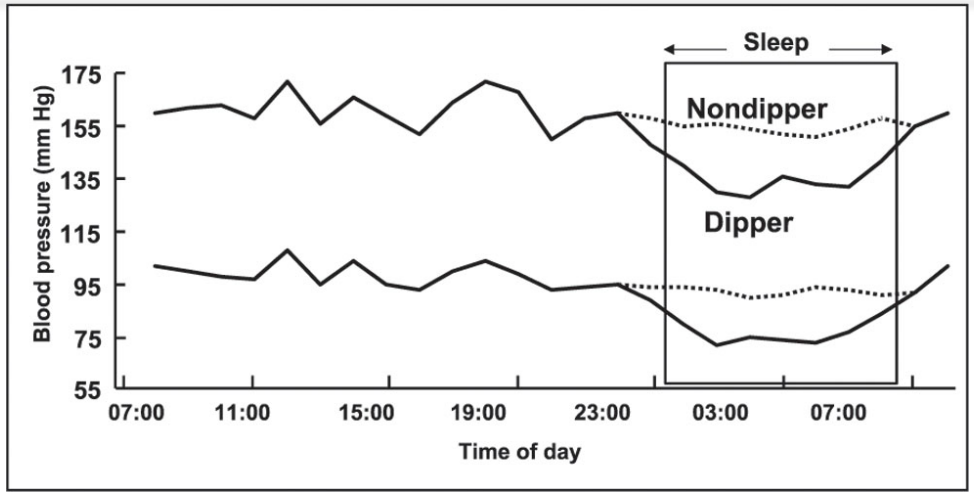
Variability in BP

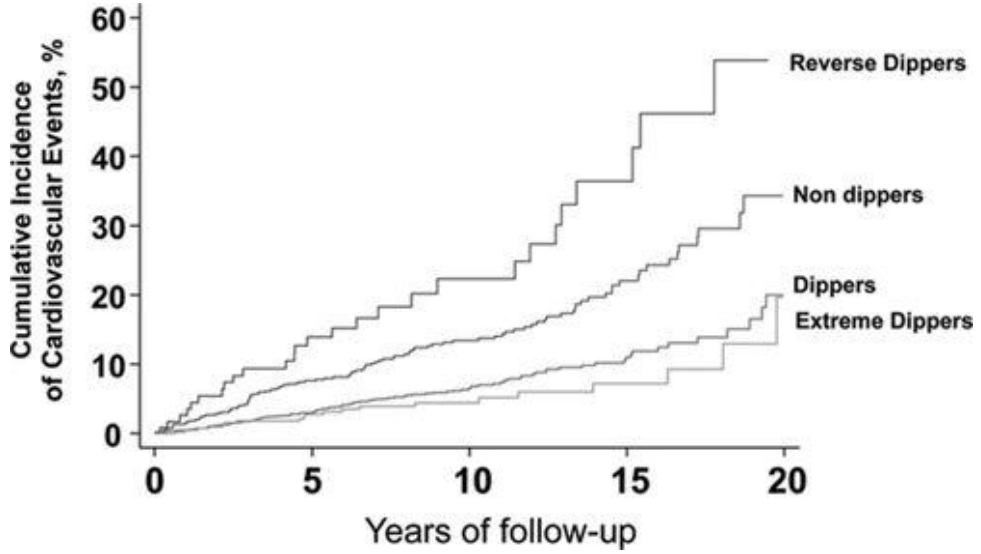
BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

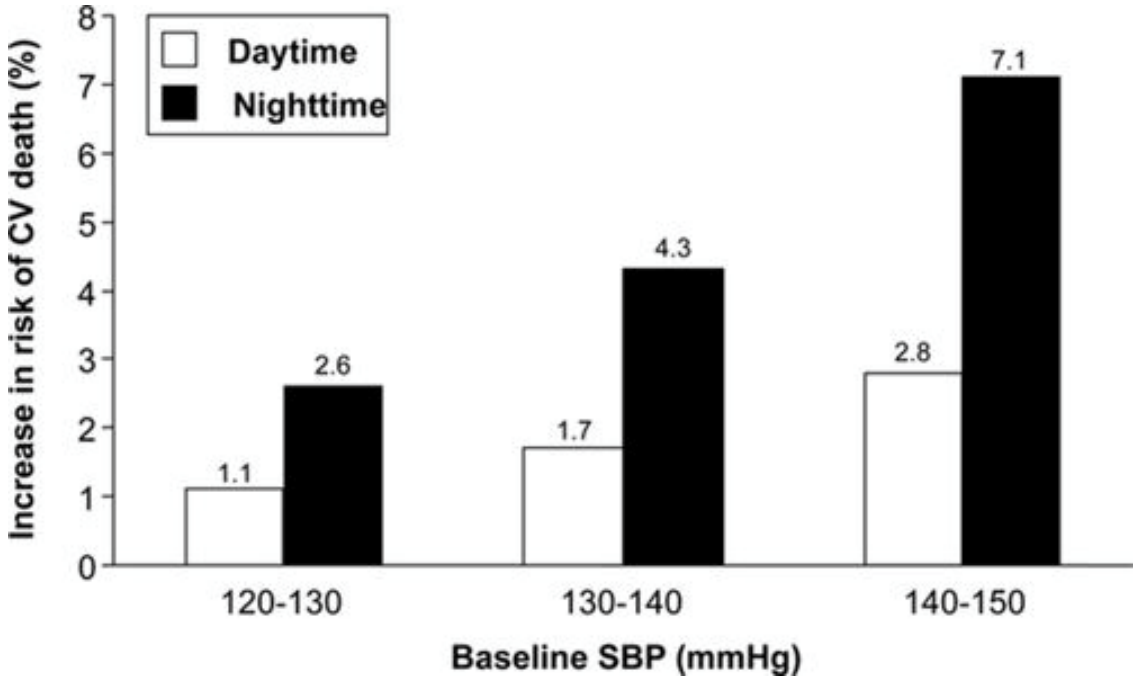
- Mean of office blood pressure readings over several visits typically utilized to direct therapy
- BP fluctuates over both short and long-term
- Episodic high values often disregarded
- Emerging evidence suggests that aberrant diurnal variation and visit-to-visit variability in BP are not merely 'noise', but carry prognostic importance

Circadian Variation in BP and CV Risk

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL







Nondipping associated with advanced age, obesity, diabetes

LaRochelle P. J Clin Hypertens. 2002; 4: 3-8.
Verdecchia P, et al. Hypertension. 2012; *60*:34–42
Sega R, et al.Circulation. 2005; *111*:1777–1783.

Nocturnal Hypertension and CV risk

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

Meta-analysis of 9 cohorts enrolling 13844 patients with hypertension

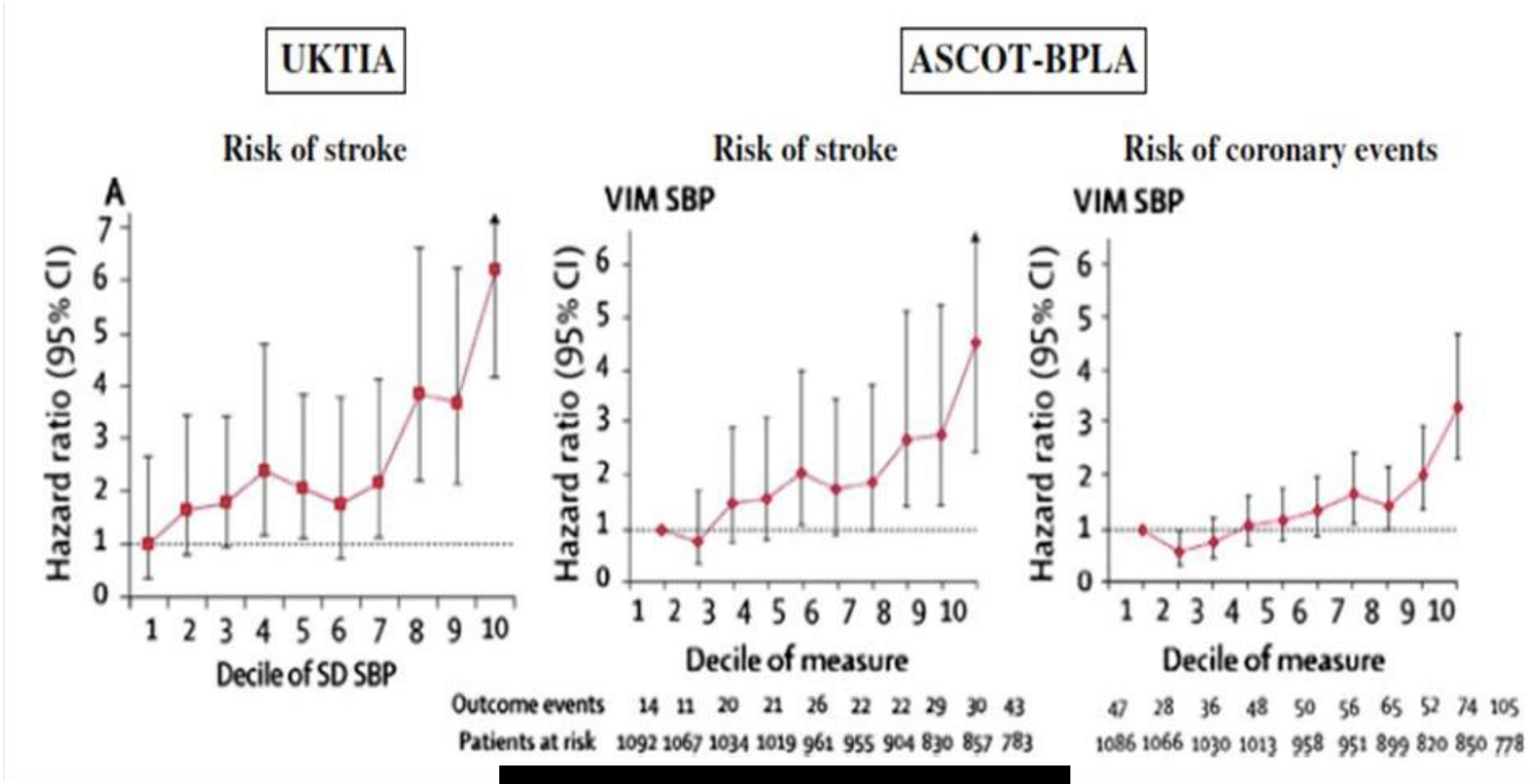
	All CV events	CAD	Stroke
Before Simultaneous Adjustment			
Nocturnal SBP	1.25 (1.22-1.29)	1.13 (1.05-1.22)	1.29 (1.19-1.39)
Daytime SBP	1.20 (1.15-1.26)	1.08 (0.99-1.18)	1.29 (1.20-1.38)
Clinic SBP	1.11 (1.06-1.16)	1.13 (0.95-1.34)	1.13 (1.06-1.21)
After simultaneous adjustment			
Nocturnal SBP	1.26 (1.20-1.31)	1.22 (1.13-1.31)	1.26 (1.09-1.46)
Daytime SBP	1.01 (0.94-1.08)	0.97 (0.88-1.07)	1.04 (0.92-1.17)
Clinic SBP	1.00 (0.95-1.05)	1.01 (0.93-1.09)	1.00 (0.97-1.03)

Greater dispersion in NSBP than DSBP or CSBP

Roush GC, et al. Journal of Hypertension 2014, 32:2332–2340

Visit-to-Visit Variability and Risk of Stroke in Hypertension

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

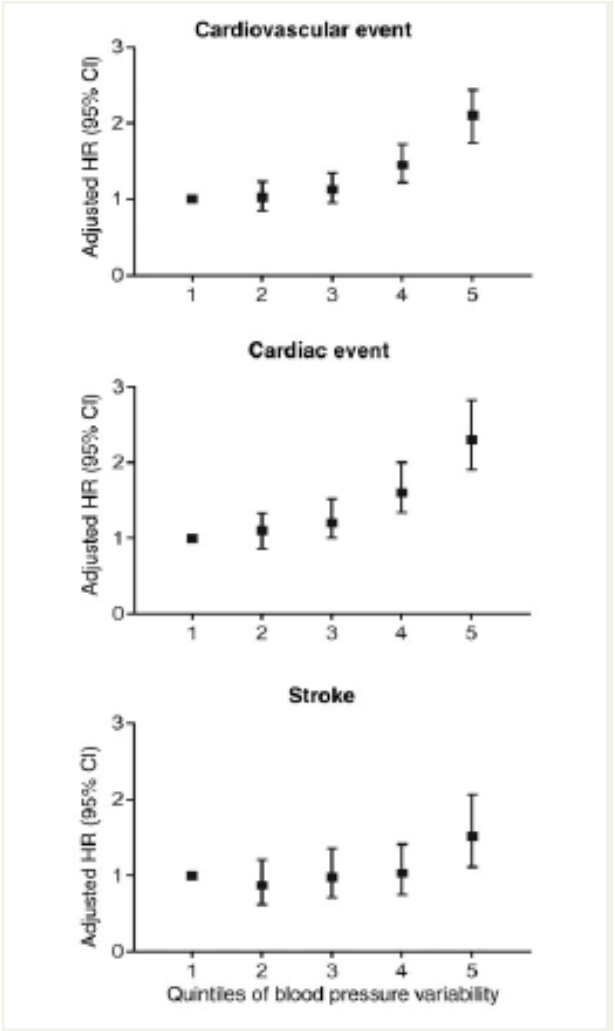


Effect independent of mean SBP

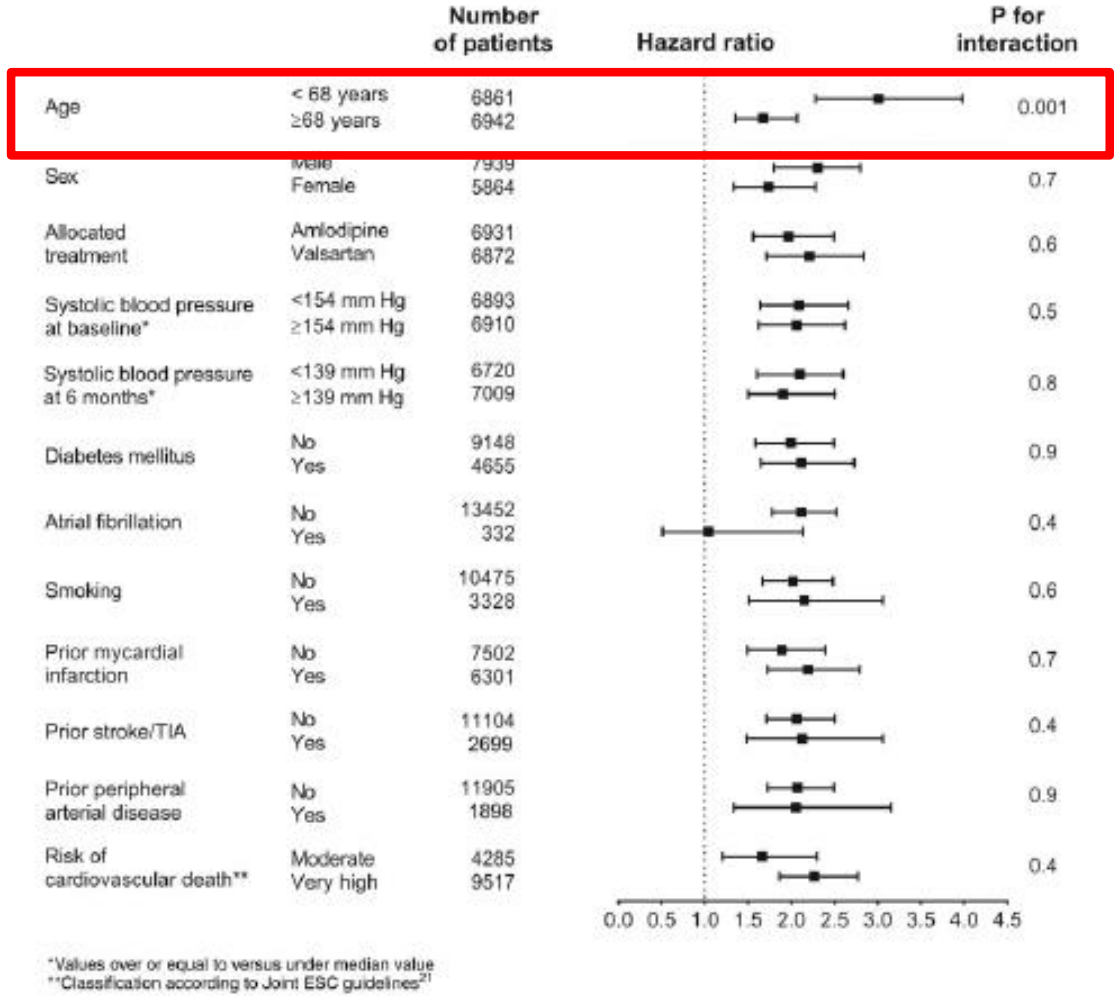
Rothwell PM, et al. Lancet 2010; 375: 895-905

Variability predicts CV events independent of baseline risk

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL



VALUE Trial (n=13803)



Mehlum MH, et al. Eur Heart J 2018;39: 2243–2251

Resistant Hypertension

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

- Uncontrolled despite >= 3 antihypertensive medications
- Variable Prevalence Depending on cohort examined

Population Based	Time Period	n	Uncontrolled With ≥3 BP Medications, %	Controlled With ≥4 BP Medications, %	aTRH, %
NHANES[13]	1988–1994	2755	8.3	1.1	9.4
NHANES[13]	1999–2004	3031	8.8	2.9	11.7
NHANES[14]	2003–2008	3710	…	…	12.8
NHANES[13]	2005–2008	2586	9.7	4.8	14.5
REGARDS[15]	2003–2007	14731	9.1	5.0	14.1
REGARDS[16] (CKD)*	2003–2007	3134	…	…	28.1
Clinic based					
EURIKA[17] (diabetes mellitus)	2009–2010	5220	13.0†	3.1	16.1
Spanish ABPM[18]	2004–2009	68045	12.2	2.6	14.8
CRIC (CKD)[19]‡	2003–2008	3939	21.2	19.2	40.4
South Carolina[20]§	2007–2010	468877	9.5	8.4	17.9
Clinical trials					
ALLHAT[21]	1994–2002‖	14684	11.5	1.2	12.7
ASCOT[22]	1998–2005	19527	48.5	…	…
ACCOMPLISH[25]	2003–2006¶	10704	39	…	…
INVEST[26]	1997–2003#	17190	25.1	12.6	37.8

Carey RM, et al. Hypertension. 2018;72:e53-e90

Factors Associated with Inadequate BP Control

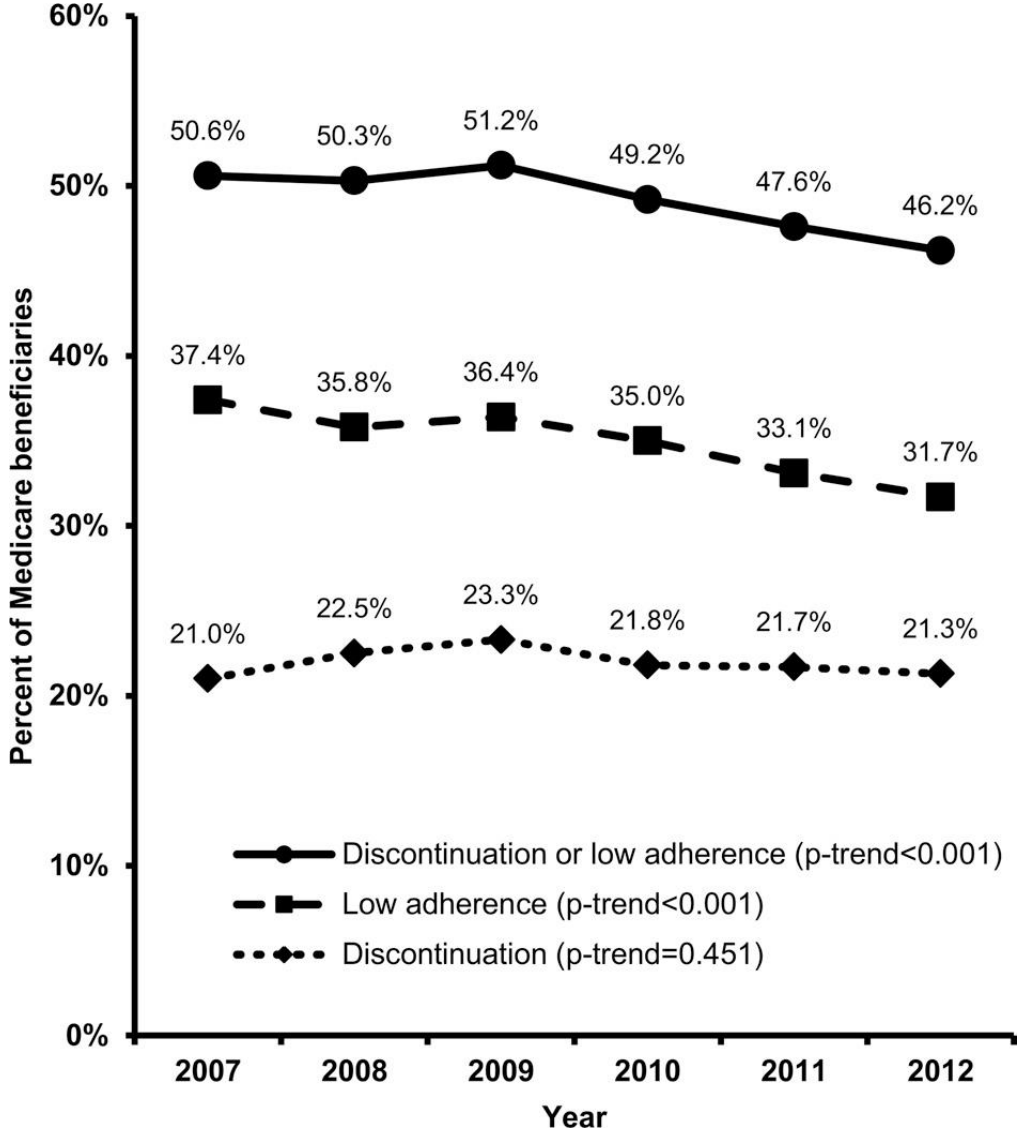
BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

- Lack of health insurance or access to care
- Absence of a usual source of care
- Failure to diagnose HTN
- Therapeutic Inertia
- Inadequate patient education
- Inadequate guidance re: lifestyle modification
- Poor adherence to treatment
- Lack of tonic control

Carey RM, et al. J Am Coll Cardiol 2018;72:1278–93

Adherence to Antihypertensive Therapy among Medicare Beneficiaries

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL



- 41135 Medicare Beneficiaries initiating antihypertensive therapy 2007-2012
- 21% of patients discontinued therapy prior to 1 year
- 31.7% of those not discontinuing therapy had low adherence to therapy (medication available for < 80% of days)

Tajeu GS, et al. Hypertension 2016;68(3):565-75

Adherence to Antihypertensive Therapy and Risk of CV Events

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

N=18806 Newly Diagnosed Hypertensives in 400 Italian Primary Care Practices

Adherence	Hazard Ratio	P-value
Low (PDC<40%)	(ref)	(ref)
Intermediate (PDC 40-79%)	0.86 (0.71-1.03)	0.109
High (PDC>=80%)	0.62 (0.40-0.96)	0.032

PDC = proportion of days covered

High adherence associated with 38% lower risk of CV events than low adherence

Mazzaglia G, et al. Circulation. 2009;120:1598-1605

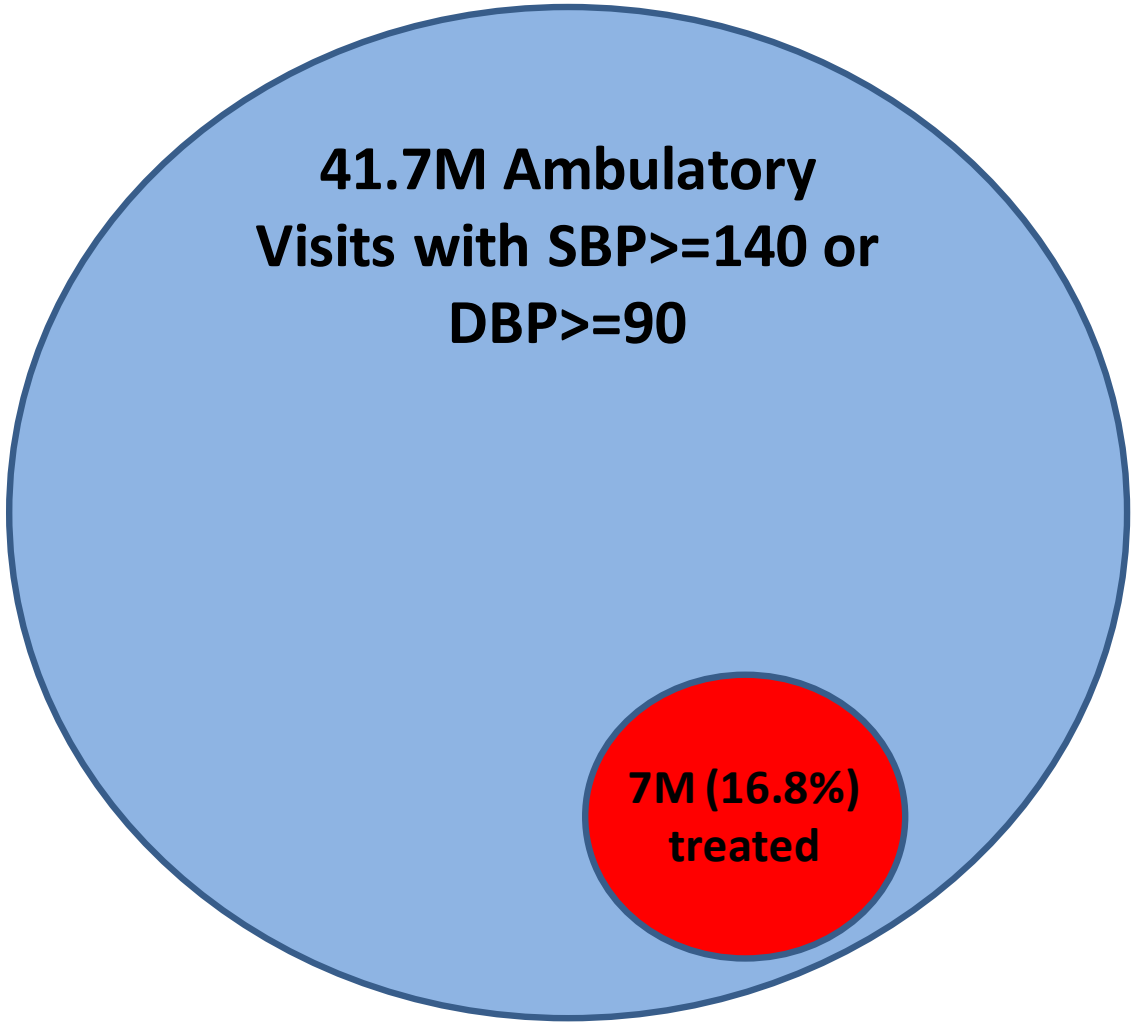
Factors Associated with Nonadherence

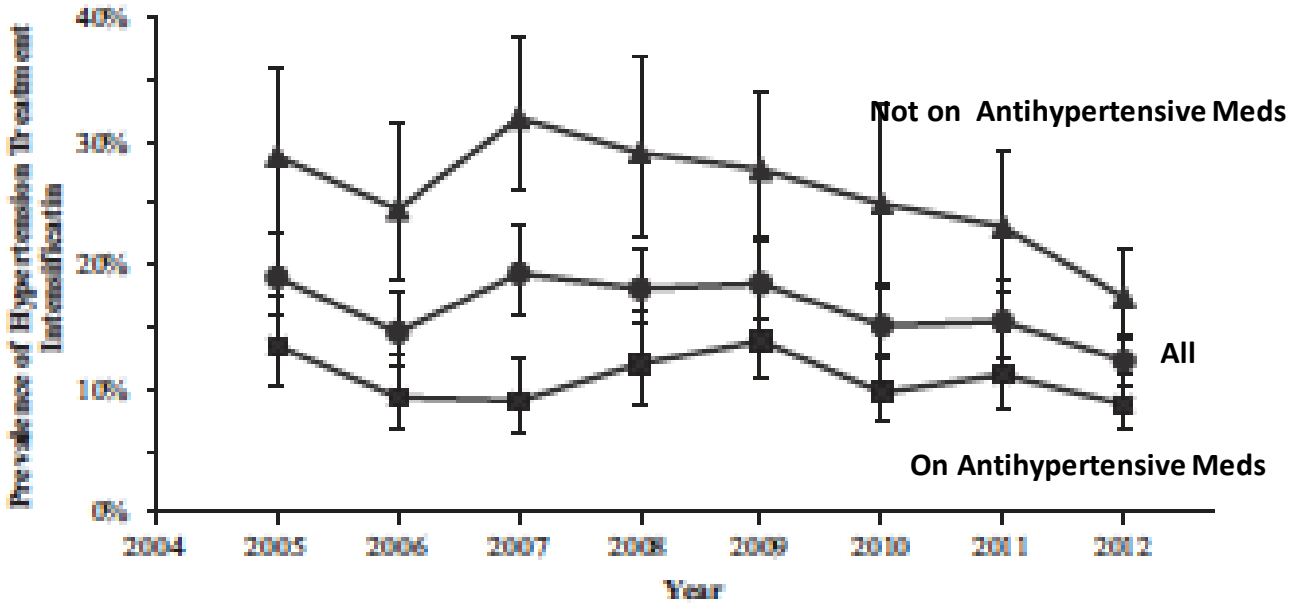
BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

- Complex Medication Regimens (Multipill regimens)
- Convenience Factors (Dosing Frequency)
- Behavioral factors
- Adverse Effects of Medication
- Younger age
- Depression
- Poor access to care

Therapeutic Inertia

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL





Possible Contributors

- Workflow Constraints/Time
- Lack of Awareness of Targets
- Concern about side effects
- Uncertainty about 'true' ambulatory BP

Mu L, Mukamal KJ. J Am Heart Assoc. 2016;5:e004188

Conclusions

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

- Continuous, graded association between SBP and risk of CV events
- Intensive BP control associated with reduction in CV events and mortality
- Large proportion of patients with hypertension are undertreated and 'resistant' hypertension is common
- Short and long-term variation in BP are associated with risk and can be modulated with pharmacologic therapy
- Nonadherence and therapeutic inertia contribute to inadequate BP control

BRIGHAM HEALTH

BRIGHAM AND WOMEN'S HOSPITAL

Thank You!

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

VOICES OF **PATIENTS & CAREGIVERS**

“The road to diagnosis was a very, very long journey. I was told that I was a drug addict, that all the pain I had been experiencing, I was making up…as an excuse to use drugs.”

Colin, living with AHP

Alnylam® PHARMACEUTICALS

Reimagining the Treatment of Hypertension with ALN-AGT

Lauren Melton, MS, MBA
Senior Director, Program Leader

Alnylam PHARMACEUTICALS

ALN-AGT Opportunity

Uncontrolled Hypertension

Disease Overview

Disease Definition

Uncontrolled hypertension defined as systolic/diastolic BP ≥130/80 mmHg, including variability, lack of night-time control, and poor adherence

Treatment resistant hypertension defined as uncontrolled BP while taking ≥3 classes of antihypertensive medications (or ≥4 regardless of BP level)[1]

Primary Hypertension[2]

~108 Million

in U.S.

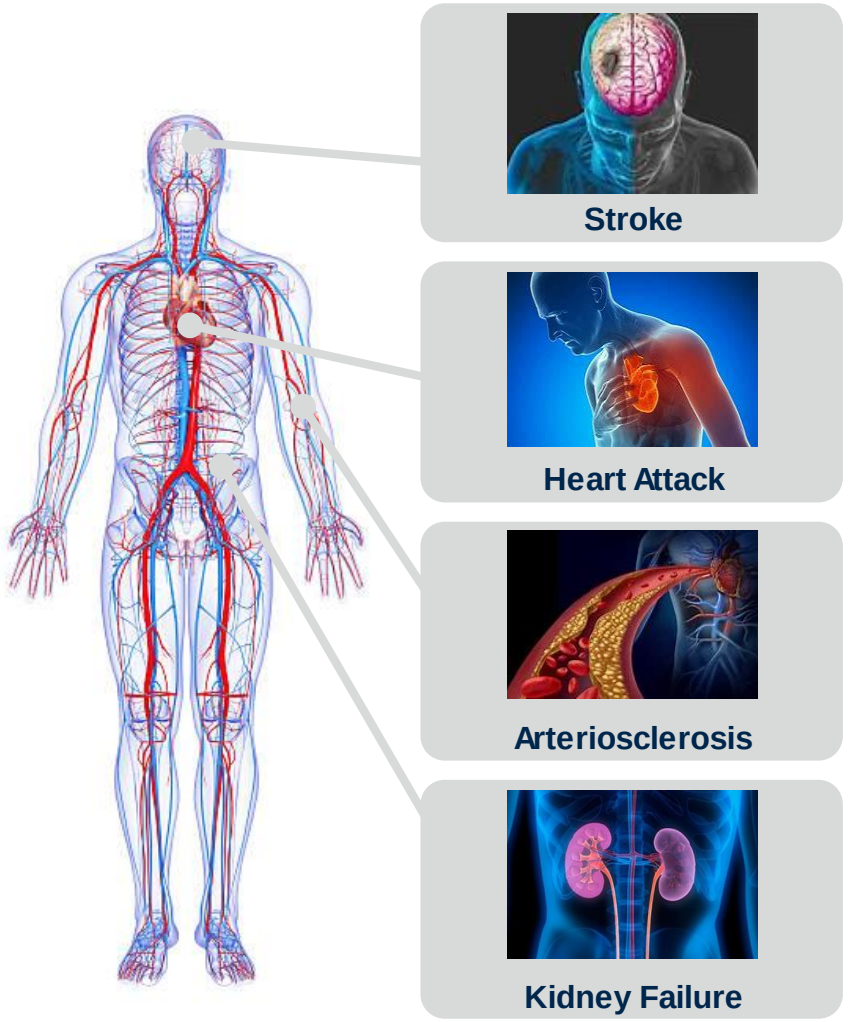
History of CVD or ≥20% 10-year ASCVD Risk (~35% of HTN)[3]

~38 Million

in U.S.

Patients with persistent hypertension despite multiple medications are at high risk for adverse cardiovascular events

Potential Complications of Hypertension



[1] https://www.ahajournals.org/doi/full/10.1161/HYP.0000000000000065

[2] Centers for Disease Control and Prevention (CDC). Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria Fro Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2013–2016external icon. Atlanta, GA: US Department of Health and Human Services; 2019.

[3] Estimated from multiple sources and internal estimates: Dorans. JAHA. 2018; Al Kibria. Hypertens Res. 2019; CDC Hypertension Cascade. 2019

NOVARTIS

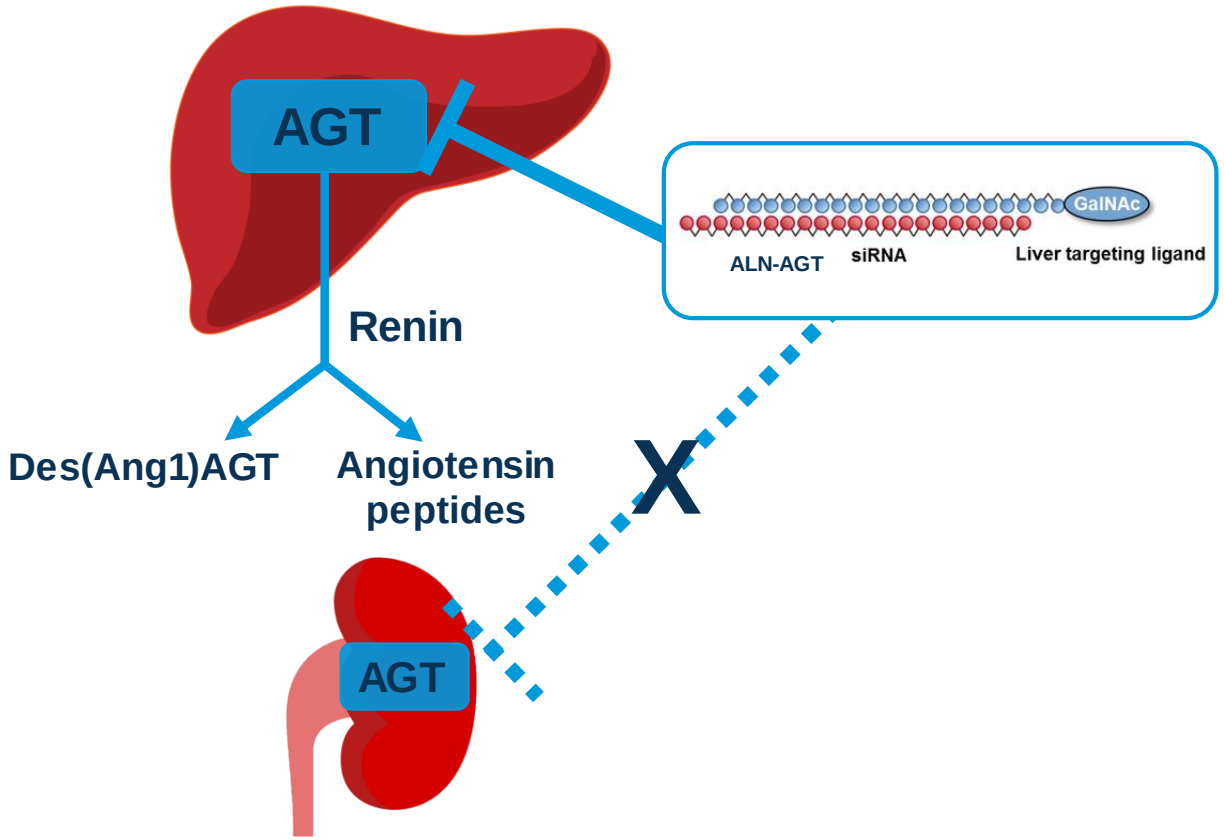
Novartis receives EU approval for Leqvio®* (inclisiran), a first-in-class siRNA to lower cholesterol with two doses a year**

Dec 11, 2020

* Product and brand name are currently under FDA review.
** After an initial dose and one at 3 months.

ALN-AGT Therapeutic Hypothesis

Liver-specific AGT knockdown



Potential Differentiated Profile to Improve Cardiovascular Health

Potential Mechanistic Advantages vs Current Therapies

- Liver-specific silencing of AGT→ improved renal safety
- Prolonged duration of action
  - Consistent and durable BP response
  - Blunting of diurnal BP variation
  - Enhanced adherence
    - Infrequent dose administration
    - Reduction in overall pill burden

AGT, angiotensinogen; BP, blood pressure; siRNA, small interfering ribonucleic acid

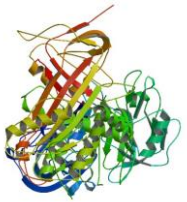
ALN-AGT for Hypertensive Diseases

Genetically Validated Target

Genetically validated, liver-expressed target gene

Biomarker for POC in Phase 1

Definable path to approval and patient access



Angiotensinogen (AGT): First Gene Linked to Primary Hypertension

Cell, Vol. 71, 169–180, October 2, 1992, Copyright © 1992 by Cell Press

Molecular Basis of Human Hypertension: Role of Angiotensinogen

Serum Biomarker
AGT levels

Clinical Biomarker
Blood Pressure

Blood Pressure

Validated Surrogate For:
Fatal and Nonfatal

Stroke

Myocardial Infarction

Jeunemaitre X et al. Cell, 1992; 2. Lifton RP, Science, 1996

ALN-AGT First-in-Human Single Ascending Dose Study

- **A total of 60 patients with hypertension completed treatment as of 16-September-2020**
- **Patients received either placebo (n=4 per cohort) or ALN-AGT (n=8 per cohort)**
- **Study conducted in outpatient setting with usual activity and dietary sodium intake**

Patient Population
(N=12 / dose cohort)

- Adults 18 to 65 years of age
- SBP >130 and ≤165 mmHg AOBP without antihypertensive meds
- 24h ABPM SBP ≥130 mm Hg
- BMI ≥18 and ≤35 kg/m^2
- Exclude secondary hypertension
- Treatment naïve or had prior antihypertensives washed out before enrollment[a]

2:1 RANDOMIZATION

- ALN-AGT 10 mg SC x 1 ✓
- ALN-AGT 25 mg SC x 1 ✓
- ALN-AGT 50 mg SC x 1 ✓
- ALN-AGT 100 mg SC x 1 ✓
- ALN-AGT 200 mg SC x 1 ✓
- ALN-AGT 400 mg SC x 1 ✓
- ALN-AGT 800 mg SC x 1 ✓

OR

- Placebo SC x 1

Primary Endpoint
- Safety and tolerability

Secondary Endpoints
- Change from baseline in serum AGT
- Plasma & Urine PK

Exploratory Endpoints
- Change from baseline in SBP/DBP by 24hr ABPM

- Additional cohorts planned to evaluate the use of ALN-AGT:
  - Controlled salt intake: tolerability in salt depletion, recovery of BP with high salt
  - Obese patients: PK/PD and effect of ALN-AGT on BP and body composition
  - Addition of ARB in background of ALN-AGT: safety and tolerability

✓ = completed cohorts

[a]Patients previously taking medication for hypertension must be without antihypertensives for ≥2 weeks prior to screening

AOBP: Automated office blood pressure; ABPM, ambulatory blood pressure monitoring; ARB, angiotensin II receptor blocker; DBP, diastolic blood pressure; PD, pharmacodynamics; PK, pharmacokinetics; SBP, systolic blood pressure; SC, subcutaneous

Demographics and Baseline Characteristics

		Placebo (N=28)	ALN-AGT Dose Cohort					
			10 mg (N=8)	25 mg (N=8)	50 mg (N=8)	100 mg (N=8)	200 mg (N=8)	400 mg (N=8)	800 mg (N=8)
Age, years; median (range)		52 (36-64)	53 (37-60)	56 (47-63)	41 (35-64)	56 (35-65)	56 (43-64)	58 (44-64)	61 (45-62)
Gender	**Male**	16	7	2	7	3	5	7	4
	Female	12	1	6	1	5	3	1	4
Race	**White**	21	6	4	3	4	6	6	6
	Black	6	1	4	4	2	2	1	2
	Asian	0	1	0	0	2	0	0	0
	Other	1	0	0	1	0	0	1	0
Blood Pressure	**24h ABPM SBP median (range)**	141 (130,154)	142 (131, 147)	141 (133, 159)	135 (113, 145)	137 (131, 153)	139 (129, 157)	139 (134, 161)	143 (132, 170)
	24h ABPM DBP median (range)	89 (75-104)	85 (77, 93)	91 (76, 104)	86 (76, 92)	86 (80, 91)	83 (76, 95)	91 (77, 100)	89 (76, 104)

Data transfer date: 27 Oct 2020

Safety & Tolerability

ALN-AGT Was Generally Well-Tolerated Supporting Continued Development

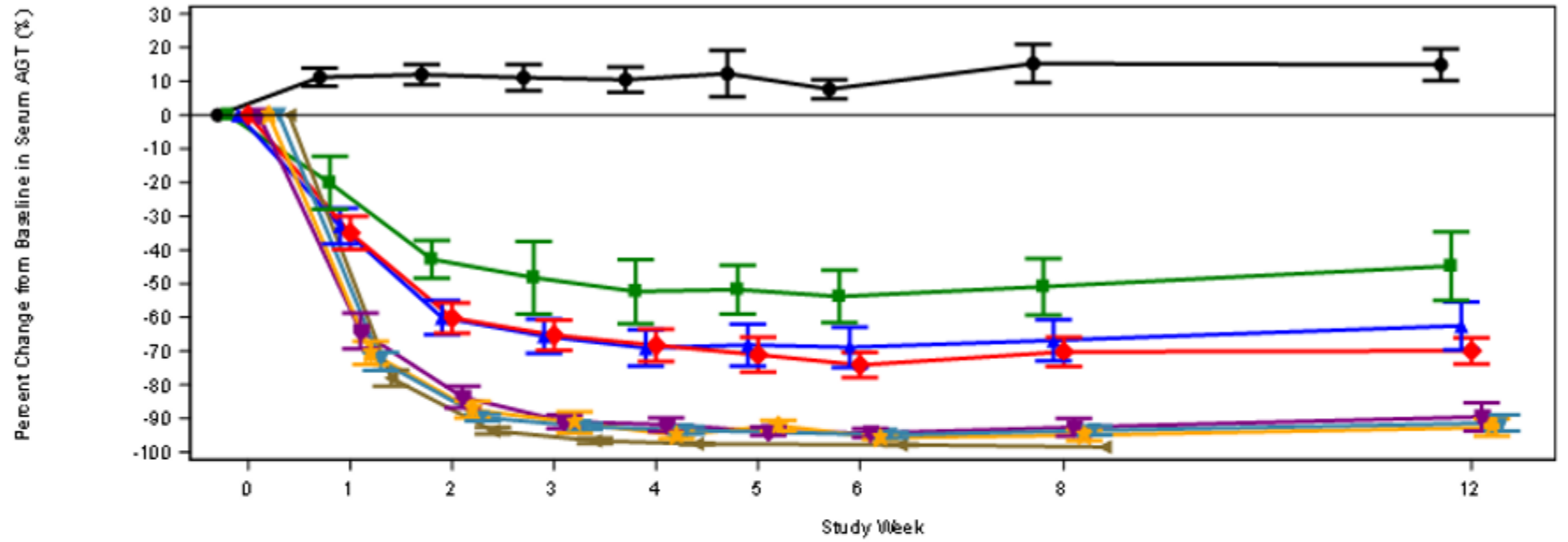
Patients Reporting an Adverse Event (AE), N	Placebo (N=28)	10 mg (N=8)	25 mg (N=8)	50 mg (N=8)	100 mg (N=8)	200 mg (N=8)	400 mg (N=8)	800 mg (N=8)
At least 1 Adverse Event	22	5	7	6	7	7	4	5
At least 1 Serious Adverse Event	1	0	0	0	0	1	0	0
At least 1 Severe Adverse Event	1	0	0	0	0	1	0	0

- Most AEs mild or moderate in severity and resolved without intervention
- No deaths or AEs leading to study withdrawal
- No treatment-related Serious AEs (SAEs)
  - Severe and serious AE of prostate cancer reported in 1 patient who received 200 mg ALN-AGT, based upon a biopsy that was performed in the screening period and reported as positive after dosing
- No patient has required intervention for low blood pressure
- No clinically significant elevations in serum ALT, serum creatinine, or serum potassium
- 5 patients with injection site reactions, all mild and transient

Data transfer date: 27 Oct 2020; AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event

Dose-Dependent AGT Lowering

- **Durable Reduction of Serum AGT >90% Sustained for 3 Months After Higher Single Doses of ALN-AGT**
- **Mean percent reduction for 800mg group (N=7) at Week 4 is 97.5% with a range of 96.2% to 98.4%**

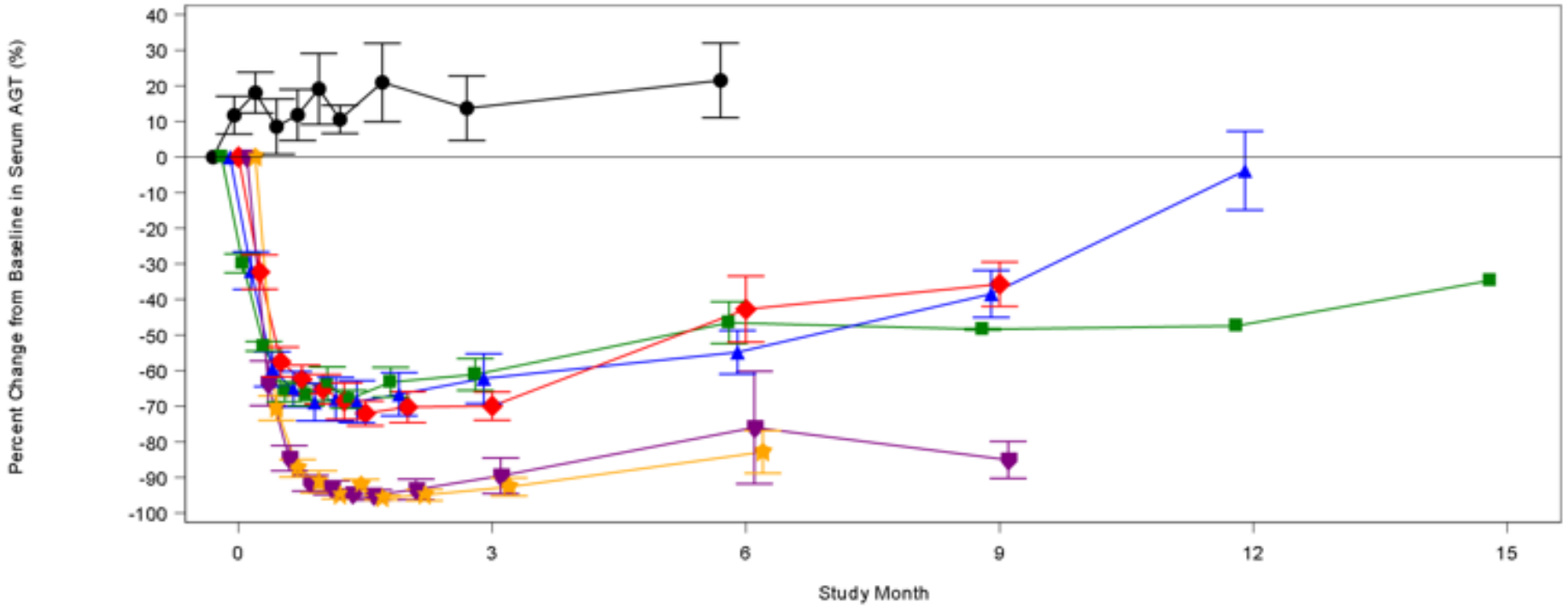


No. of Patients:									
Placebo	28	27	28	28	26	17	23	23	24
10 mg ALN-AGT01	8	8	8	8	8	8	8	8	8
25 mg ALN-AGT01	8	8	8	8	8	8	8	8	8
50 mg ALN-AGT01	8	8	8	8	8	8	8	7	7
100 mg ALN-AGT01	8	7	8	8	8	8	8	8	7
200 mg ALN-AGT01	8	8	8	7	6	2	3	7	8
400 mg ALN-AGT01	8	8	8	8	8	0	8	8	8
800 mg ALN-AGT01	8	8	8	5	7	0	3	1	0

Data transfer date: 08 Dec 2020

AGT Lowering During Long Term Follow up

Serum AGT Reduction Continues Beyond 3 Months After Single Doses of ALN-AGT

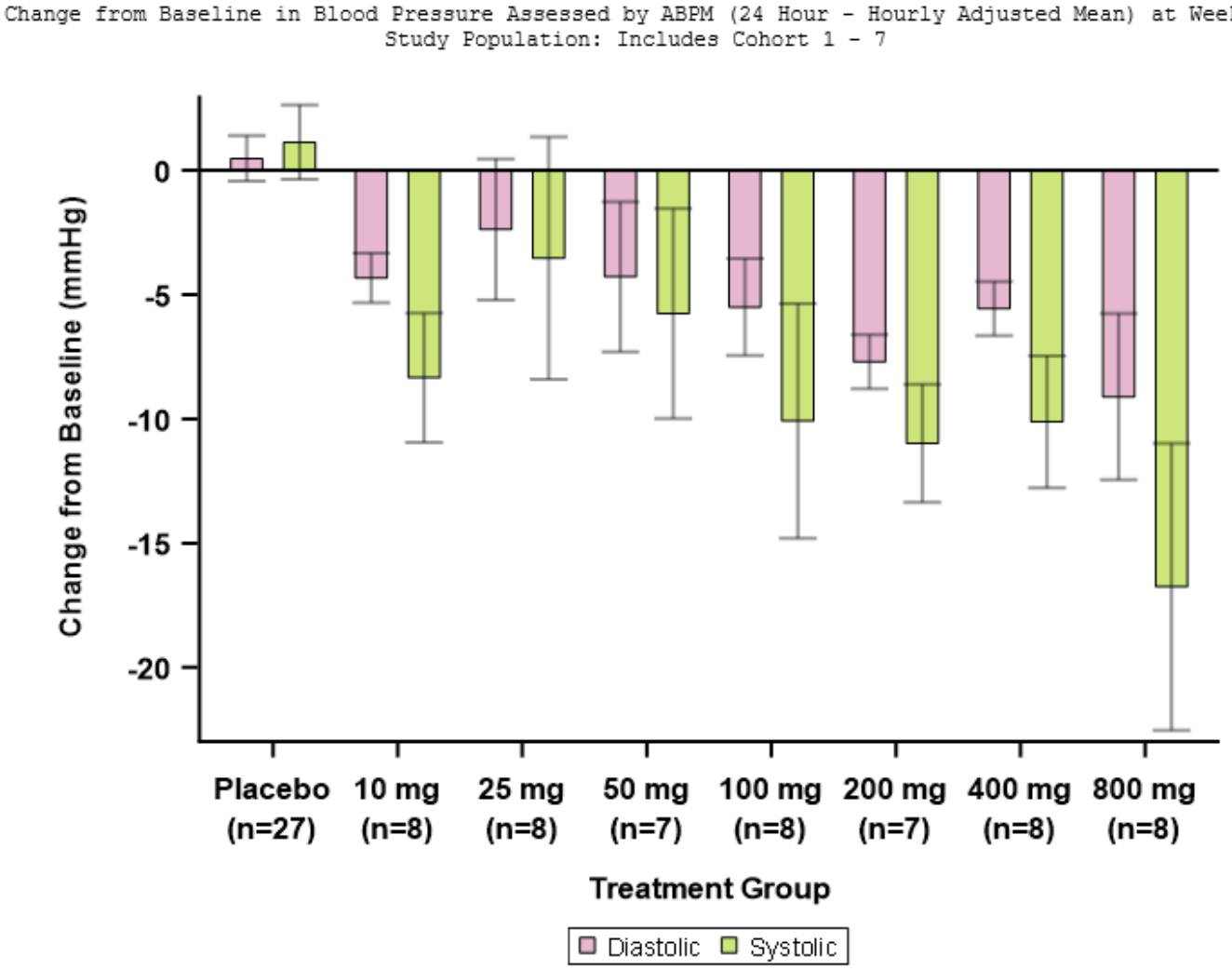


No. of Patients:						
Placebo	11	11	11	0	0	0
10 mg ALN-AGT01	5	5	5	2	1	1
25 mg ALN-AGT01	8	8	8	6	6	0
50 mg ALN-AGT01	7	7	7	4	0	0
100 mg ALN-AGT01	7	6	7	5	0	0
200 mg ALN-AGT01	8	8	8	0	0	0

Data transfer date: 27 Oct 2020

Dose-Dependent Reductions in SBP and DBP

24h SBP Reduction >15 mm Hg at 8 Weeks After 800mg Single Dose of ALN-AGT Monotherapy



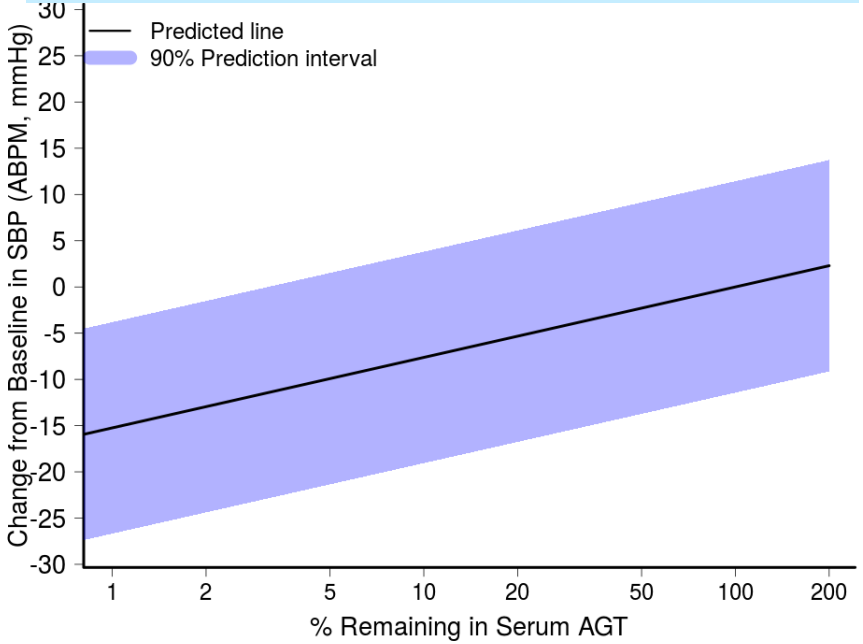
800 mg cohort (N=8) at Week 8:

- Mean systolic blood pressure reduction is **16.8 mmHg**
- Mean diastolic blood pressure reduction is **9.1 mmHg**

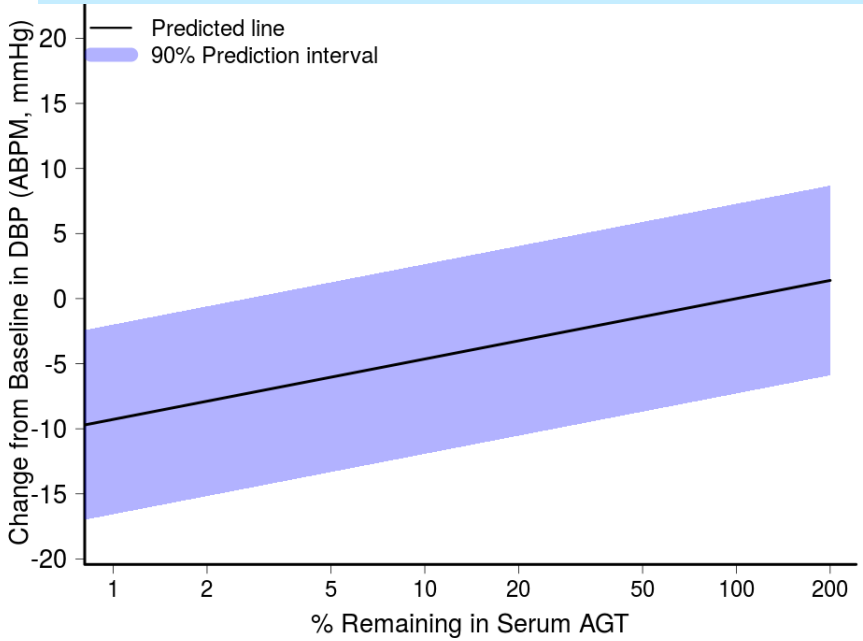
Data access date: 19 Nov 2020; SBP: systolic blood pressure; DBP: diastolic blood pressure

Model Predicted Serum AGT Reduction versus 24-h ABPM Relationship

AGT Reduction vs. Change in SBP



AGT Reduction vs. Change in DBP



Model Predictions		
AGT Reduction	**SBP change (mmHg)**	**DBP change (mmHg)**
50%	-2.3	-1.4
90%	-7.6	-4.6
95%	-9.9	-6.0
97%	-11.6	-7.1

ABPM: ambulatory blood pressure monitoring; SBP: systolic blood pressure; DBP: diastolic blood pressure

Target Patient Populations Under Consideration for ALN-AGT

Long-acting therapeutic is expected to have significant value given poor adherence and physician inertia to treat early in disease progression, across a continuum of patient segments

Uncontrolled HTN with High CV Risk

- High unmet need in vulnerable population
- ALN-AGT must be safe and effective when used in combination with major classes of standard of care medications
- Potential for uptake in resistant hypertension with appropriate supportive data

Broad HTN Including 1st Line Use

- Low adherence limits clinical benefit of widely available oral generics
- Infrequently administered antihypertensive could provide foundational control of blood pressure

HTN Preventive Treatment

- ~28% of the US adult population considered "pre-hypertensive"[1]
- Early intervention is in line with current treatment trends in healthcare
- Potential to position Alnylam as a pioneer in the new age of population health medicine

- 1 Booth. Hypertension. 2017 Aug;70(2): 275–284.

Clinical Development Considerations

Drugs indicated to treat hypertension to lower blood pressure: FDA Guidance recommends to include in label indication, "Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions."[1]

Well-Established Endpoints:

- Systolic and diastolic BP by clinic blood pressure
- 24 Hour mean systolic and diastolic BP by ambulatory blood pressure monitoring (ABPM)

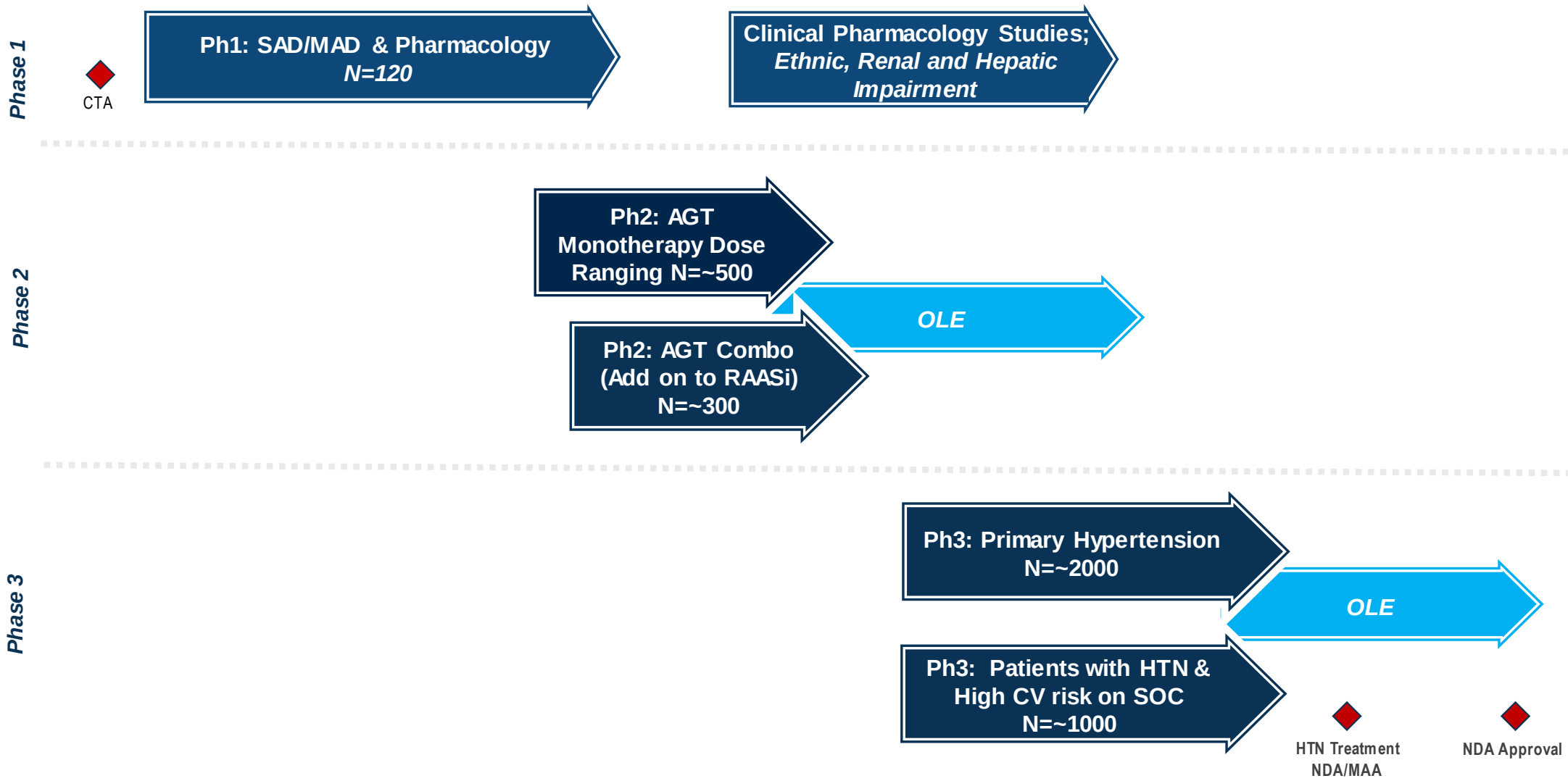
Opportunity for Novel Endpoints Subject to Alignment with Regulators:

- BP variability
- Night-time BP and night-time dip
- Improved adherence/ compliance (real-world pragmatic study)

[1] For complete recommendation on FDA labeling of indications for use of drugs to treat hypertension, including potential statements that no controlled trials demonstrating risk reduction have been conducted, see https://www.fda.gov/regulatory-information/search-fda-guidance-documents/hypertension-indication-drug-labeling-cardiovascular-outcome-claims

HTN: hypertension; CV: cardiovascular; BP: blood pressure

Initial DRAFT CDP: Broad Spectrum of HTN Patient Populations



15 SAD/MAD: single or multiple ascending doses; RAASi: renin angiotensin aldosterone system inhibitor; OLE: open label extension; SOC: standard of care

ALN-AGT Expected Phase 2 Trial Schemas in HTN

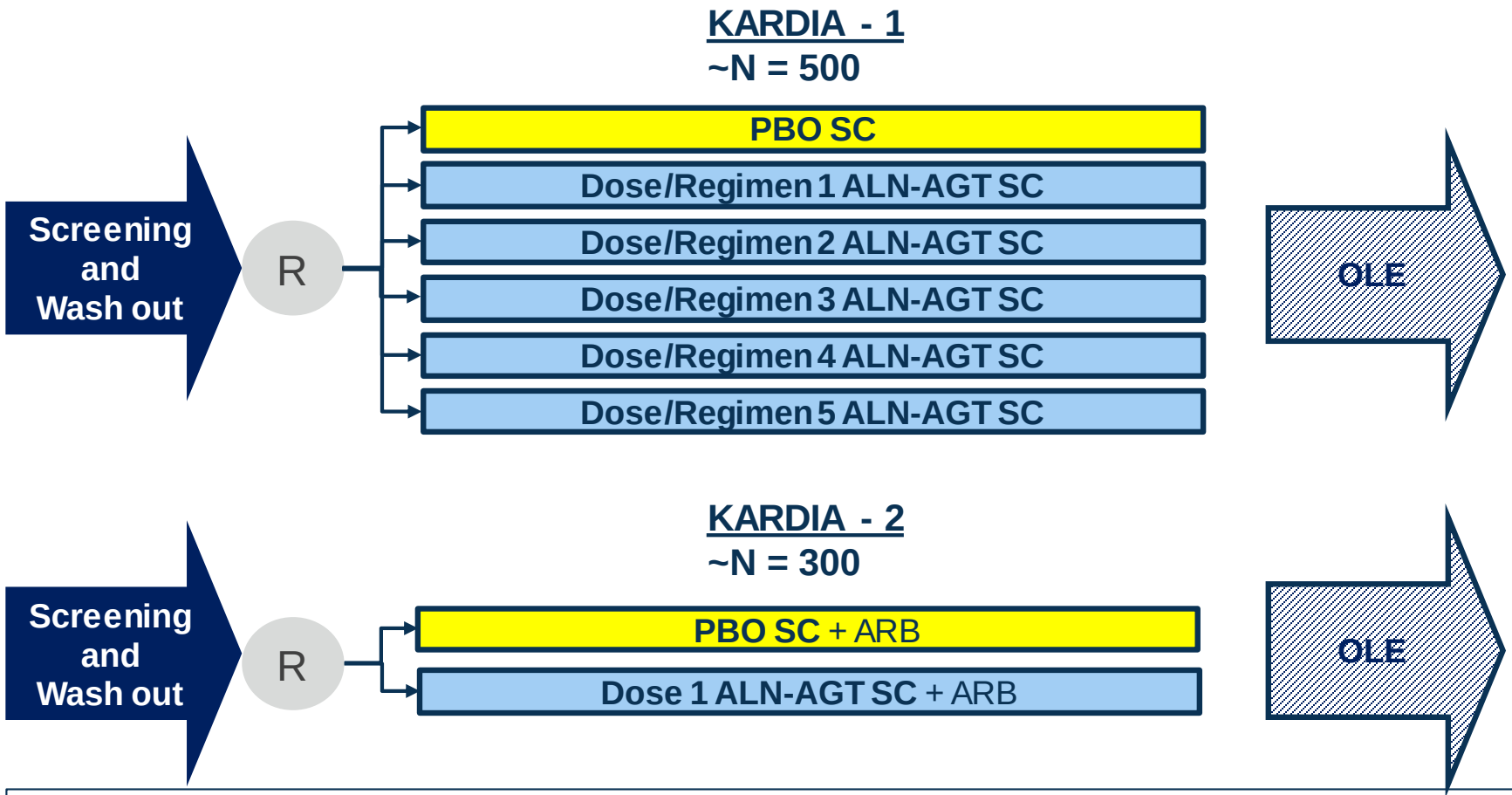
KARDIA-1 and KARDIA-2 to initiate in Mid-2021

***Expected* Patient Population**

- Adults 18 to 75 years of age with primary hypertension
- Treatment naïve or had prior antihypertensives washed out before enrollment

***Expected* Primary Efficacy Endpoint**

- Change from baseline in systolic blood pressure as compared to placebo



- Study 1 to test antihypertensive effect of ALN-AGT monotherapy with placebo control
  - Dose regimens of q3m and q6m will be tested
- Study 2 investigates ALN-AGT as an add-on to conventional antihypertensive therapy

R: randomization; SC: subcutaneous; OLE: open label extension; ARB: angiotensinII receptor blocker

ALN-AGT Commercial Opportunity: High Risk for Cardiovascular Events

Patients with Uncontrolled Blood Pressure at High Risk for Adverse CV Events

PREVALENCE

- ~38M patients in U.S. with high CV risk and HTN; **~20M have uncontrolled BP** on current regimen[1]
- High CV risk defined ≥20% 10-year **ASCVD risk or previous history** of myocardial infarction, angina, stroke, transient ischemic attack, heart failure, peripheral arterial disease, type 2 diabetes

CURRENT TREATMENT LANDSCAPE

- **Guidelines specify treatment of HTN based on clinical severity and/or comorbidities**
- Patients initiated on mono or combo therapy; increased doses or additional agents added if BP not controlled
- **Uncontrolled HTN often due to non-adherence** of prescribed therapy given daily pill burden[2]

DISEASE BURDEN

- Uncontrolled hypertension is the **major risk factor for CV disease** morbidity and mortality[3]
- ~1.5M people in U.S. have myocardial infarction or stroke annually, with ~50% of these major adverse cardiovascular events attributed to HTN[4,5]

COST BURDEN

- Annual direct and indirect cost of hypertensive disease and stroke in U.S.[6]: $55B and 45B*
- **Suboptimal BP control cost $370B globally in 2001** (~10% of world's overall healthcare expenditure at that time[7])

Treatment of Uncontrolled Blood Pressure in Patients with High CV Risk

>$4B potential global market opportunity at peak

[1] Estimated based on historical rates of CV events: myocardial infarction, angina, stroke, transient ischemic attack, heart failure, peripheral arterial disease, type 2 diabetes. Sources: Virani et al, Circulation. 2020;141:e139–e596. Mainous et al, Am J Prev Med 2018;55(3):384–388. Sonawane et al, J Clin Hypertens. 2019;21:766–773. Gu et al, Circulation. 2012;126:2105-2114. Gu et al, Clin Med Insights Cardiol. 2019;13:1–9. Dorans. JAHA. 2018; Al Kibria. Hypertens Res. 2019; CDC Hypertension Cascade. 2019 National Diabetes Statistics report 2020. 2018 USRDS Annual Data Report. US Census Bureau. TriNetX USA Network, accessed May 2020. Estimate of ~50% of patients diagnosed with HTN and high CV risk are uncontrolled

[3] Zhou. Sci Rep. 2018; [4] Lawes. Lancet. 2001. [5] Korsnes. JMCP. 2015; [6] Benjamin. Circulation. 2019; [7] Gaziano. J Hypertens. 2009

- Not all stroke costs are associated with hypertension; additional cost related to heart disease and hypertension are observed

ASCVD: Atherosclerotic Cardiovascular Disease, CV: cardiovascular; BP: blood pressure; HTN: hypertension

ALN-AGT Commercial Opportunity: Primary Hypertension

Potential foundational antihypertensive requiring infrequent dosing

PREVALENCE

- ~108M patients in U.S. have HTN
- Despite the availability of multiple classes of antihypertensive medications, **~75% of hypertensive patients do not achieve controlled blood pressure**[1]

CURRENT TREATMENT LANDSCAPE

- Guidelines specify treatment of HTN based on clinical severity and/or comorbidities
- Patients initiated on mono or combo therapy; increased doses or additional agents added if BP not controlled
- Uncontrolled HTN often due to non-adherence of prescribed therapy given daily pill burden[2]

DISEASE BURDEN

- Uncontrolled hypertension is the major risk factor for CV disease morbidity and mortality[3]
- ~1.5M people in U.S. have myocardial infarction or stroke annually, with **~50% of these major adverse cardiovascular events attributed to HTN**[4,5]

COST BURDEN

- Annual direct and indirect cost of hypertensive disease and stroke in U.S.[6]: $55B and 45B*
- **Suboptimal BP control** cost $370B globally in 2001 (~10% of world's overall healthcare expenditure at that time[7])

Treatment of Uncontrolled Blood Pressure in Patients with Primary Hypertension

>$4B potential global market opportunity at peak

[1] Centers for Disease Control and Prevention (CDC). Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria From the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2013–2016external icon. Atlanta, GA: US Department of Health and Human Services; 2019.

[3] Zhou. Sci Rep. 2018; [4] Lawes. Lancet. 2001. [5] Korsnes. JMCP. 2015; [6] Benjamin. Circulation. 2019; [7] Gaziano. J Hypertens. 2009

* Not all stroke costs are associated with hypertension; additional cost related to heart disease and hypertension are observed

Summary and Next Steps in Development of ALN-AGT

Significant unmet need for treatment of hypertension in patients with uncontrolled blood pressure

- Sustained blood pressure control with infrequent dosing could benefit patients with difficult to treat hypertension or patients at risk for CV events with uncontrolled blood pressure and could be a foundational antihypertensive treatment for patients with primary hypertension

Initial data from ongoing Phase 1 study in patients with mild to moderate hypertension encouraging

- Encouraging safety and tolerability profile
- >10 mmHg persistent reduction in mean 24-h systolic blood pressure
- Durability supportive of once quarterly and possibly less frequent dosing
- Additional Phase 1 clinical data expected in 2021

Initiation of Phase 2 KARDIA Studies

- Studies planned for mid-2021; will explore use of ALN-AGT both alone and in combination with SOC antihypertensives

VOICES OF **PATIENTS & CAREGIVERS**

“I’ve often thought back about what we did for the first 2 years of her life. Daily dialysis… sometimes up to 15 hours a day almost seems unthinkable!”

A caregiver of a PH1 patient; quote featured in Patient Perspectives article

Alnylam® PHARMACEUTICALS

Alnylam PHARMACEUTICALS