Patisiran & Vutrisiran, in Development for the Treatment of Transthyretin-Mediated Amyloidosis

RNAi ROUNDTABLE 2019

September 16, 2019

Alnylam® PHARMACEUTICALS

Agenda

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

Introduction and ONPATTRO® (patisiran)
- Eric Green – Senior Vice President, General Manager, TTR Program

ONPATTRO Patient Ambassador
- Mike – Patient Diagnosed with hATTR Amyloidosis

Patisiran Development Program
- John Vest, M.D. – Executive Director, Clinical Research

Vutrisiran (ALN-TTRsc02) Development Program
- Rena Denoncourt – Senior Director, Program Leader, Vutrisiran Program

Alnylam's TTR Franchise
- Eric Green – Senior Vice President, General Manager, TTR Program

Q&A Session

Reminders

Event will run for approximately 60-75 minutes

Q&A session at end of presentation

- Questions may be submitted at any time via the ‘Ask a Question’ field on the webcast interface

Replay, slides and transcript available at www.alnylam.com/capella

Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies, including with respect to patisiran and vutrisiran; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; the timing of regulatory submissions for our product candidates, including patisiran and vutrisiran, and our ability to obtain and maintain regulatory approval, pricing and reimbursement for such products; our progress in establishing a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally, including ONPATTRO®, and patisiran and vutrisiran if approved for by regulatory agencies; 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, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors or risks 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.

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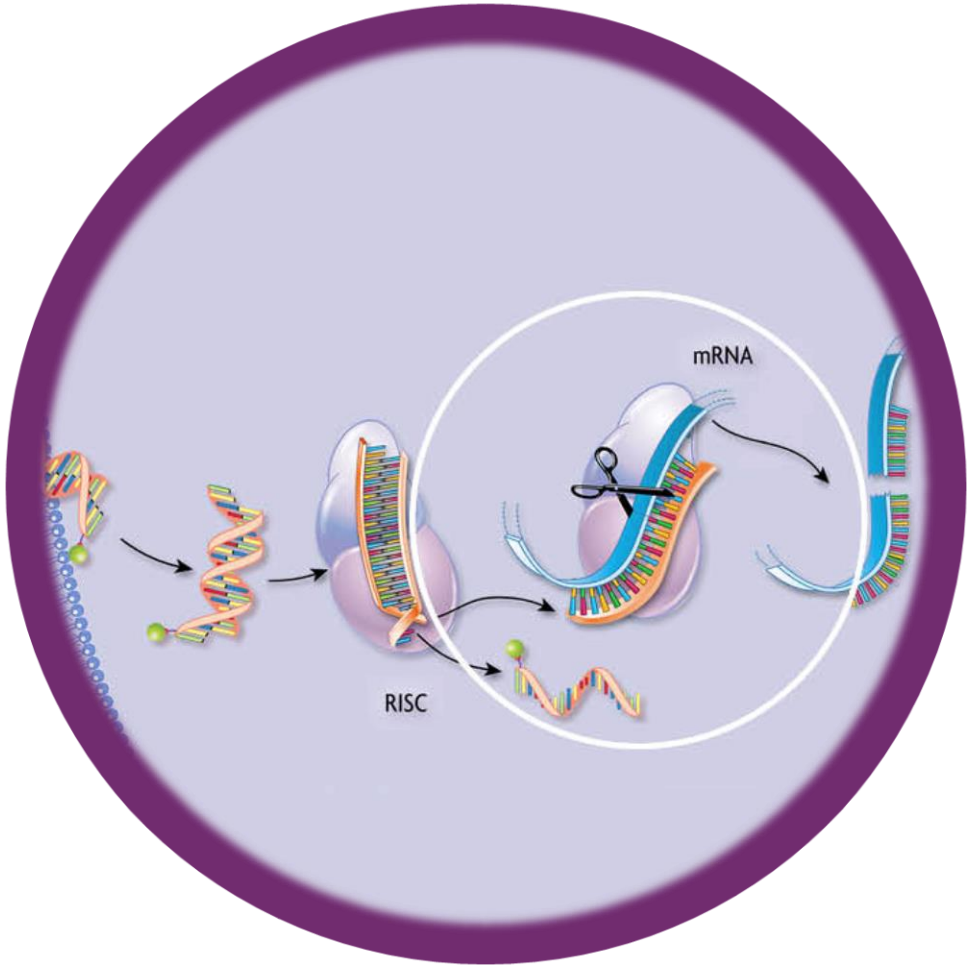
RNAi Therapeutics: New Class of Innovative Medicines

Clinically Proven Approach with Transformational Potential

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



Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

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

		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	EARLY STAGE (IND or CTA Filed-Phase 2)	LATE STAGE (Phase 2-Phase 4)	REGISTRATION/ COMMERCIAL[3]	COMMERCIAL RIGHTS
onpattro (patisiran) lipid complex injection 10 mg/5 mL	*hATTR Amyloidosis*[2]	✓	●			●	Global
Givosiran	*Acute Hepatic Porphyria*	✓	●			●	Global
Patisiran	*ATTR Amyloidosis Label Expansion*	✓			●		Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*	✓			●		15-30% royalties
Inclisiran	*Hypercholesterolemia*	✓			●		Milestones & up to 20% royalties
Lumasiran	*Primary Hyperoxaluria Type 1*	✓	●		●		Global
Vutrisiran	*ATTR Amyloidosis*	✓			●		Global
Cemdisiran	*Complement-Mediated Diseases*	✓		●			50-50
Cemdisiran/Pozelimab Combo[4]	*Complement-Mediated Diseases*			●			Milestone/Royalty
ALN-AAT02	*Alpha-1 Liver Disease*			●			Global
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*			●			50-50 option rights post-Phase 2
ALN-AGT	*Hypertension*			●			Global

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

ATTR Amyloidosis

Rare, Progressively Debilitating, and Often Fatal Disease

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

Hereditary ATTR (hATTR) Amyloidosis

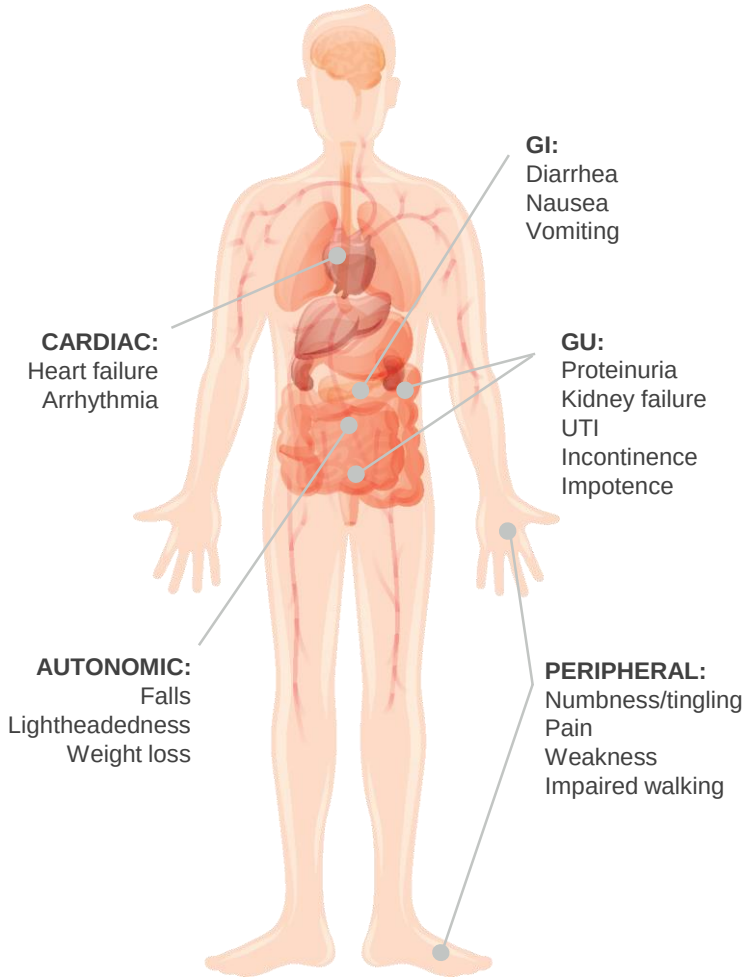
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

patients worldwide



[1] Coelho T, et al. N Engl J Med. 2013;369(9):819-829

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

Diagnostic Tools for ATTR Amyloidosis

Assessment of Multisystem Involvement, Confirmatory and Non-Confirmatory Options

Potential Manifestations

Progressive Decline in Cardiac Function

Progressive Decline in Physical Function

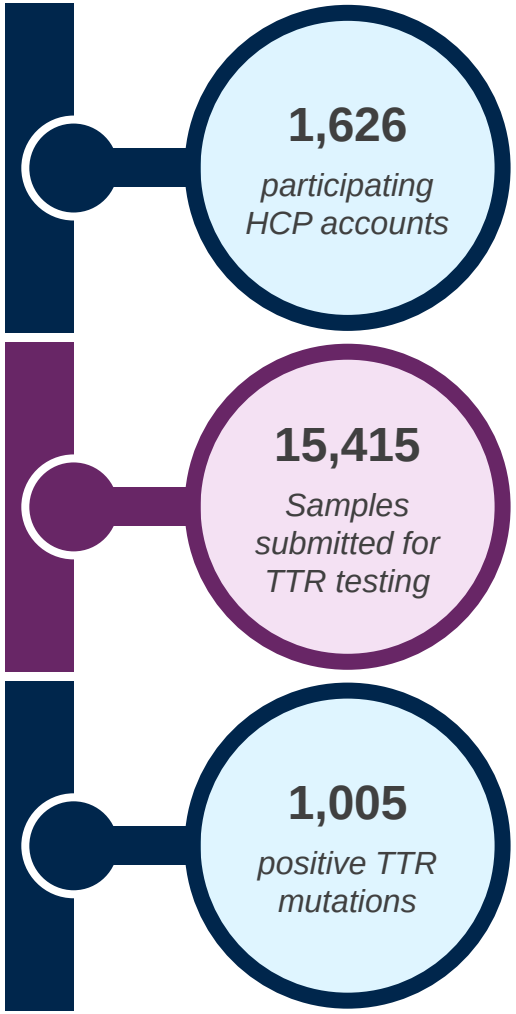
Progressive Polyneuropathy: Pain, Motor Weakness, and Autonomic Dysfunction

	Polyneuropathy Assessments	Cardiomyopathy Assessments
Non-Confirmatory	Quantitative Sensory Testing (QST) EMG / Nerve Conduction	EKG Echocardiogram Cardiac MRI
Confirmatory	Genetic Testing Tissue Biopsy	Genetic Testing Tissue Biopsy Scintigraphy

EMG – electromyography; EKG – electrocardiogram; MRI – magnetic resonance imaging

Alnylam Act® – TTR Amyloidosis

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



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

Tests and services are performed by independent third parties

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

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

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

Data as of July 2019

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

Collaboration with 23andMe

Increasing Awareness with Direct-to-Consumer Tests

23andMe offers direct-to-consumer genetic testing that provides consumers with information about health, ancestry, traits and more, including whether they carry genetic markers that could influence certain health conditions

Collaboration Objectives

1. Drive awareness of hATTR amyloidosis and resources available to people who may be at risk for the disease[1]
2. Enable those who may be at risk to make more informed decisions about their health
3. Reinforce Alnylam's commitment to the hATTR amyloidosis community

Alnylam's collaboration enables all eligible 23andMe customers, if they opt in to the Hereditary Amyloidosis (TTR-Related) Genetic Health Risk Report, to be notified if they are a carrier of a V122I, V30M or T60A mutation (the three most common TTR mutations in the U.S.) and to receive more information about the disease[2]

- 23andMe's Hereditary Amyloidosis (TTR-Related) Genetic Health Risk Report launched in April 2019
  - This report is available to customers in the U.S., Canada, Denmark, Finland, Ireland, Sweden and the Netherlands

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

- This program went live in July 2019
- **>500 kits** already supplied through program[3]

[1] 23andMe Health + Ancestry Service is intended for use in adults to report genetic variants associated with a higher risk of developing a disease. Not intended to diagnose any disease or describe overall risk of developing a disease. Visit 23andme.com/testinfo for additional information about each report; [2] 23andMe does not share customers' individual-level data, personal health informa ion, or personally identifiable information with Alnylam. [3] Data as of 31Aug2019

RNAi Therapeutic Hypothesis in ATTR Amyloidosis

Silencing TTR Gene Expression Can Potentially Address Underlying Cause of Disease

Production of mutant and wild type TTR in liver*

Reduce
circulating TTR

Prevent or clear
tissue amyloid deposits

Halt or improve
progressive manifestations of disease

RNAi Therapeutic Hypothesis

siRNA sequence selected to silence both mutant and wild type TTR

* >95% of TTR in circulation produced in liver

The first RNAi therapeutic is

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

onpattro®

(patisiran) lipid complex injection 10 mg/5 mL

onpattro®

2 mg/mL concentrate for solution for infusion patisiran

オンパットロ®

パチシランナトリウム注射液2mg/mL

ONPATTRO® – Major Market Approvals and Submissions

U.S.	*August 10, 2018*	For the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults	onpattro (patisiran) lipid complex injection 10 mg/5 mL
EU	*August 27, 2018*	For the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults with stage 1 or stage 2 polyneuropathy	onpattro 2 mg/mL concentrate for solution for infusion patisiran
Canada	*June 7, 2019*	For the treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis)	onpattro (patisiran) lipid complex injection 10 mg/5 mL
Japan	*June 18, 2019*	For the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy	オンパットロ® パチシランナトリウム注射液2mg/mL

Switzerland Filing

MAA submitted December 2018

Israel Filing

MAA submitted June 2019

Brazil Filing

NDA planned late 2019

hATTR Amyloidosis Market Opportunity

Estimated Disease Prevalence*†

~ 50,000 patients worldwide

NEUROLOGIC PHENOTYPE
> 50% have cardiomyopathy

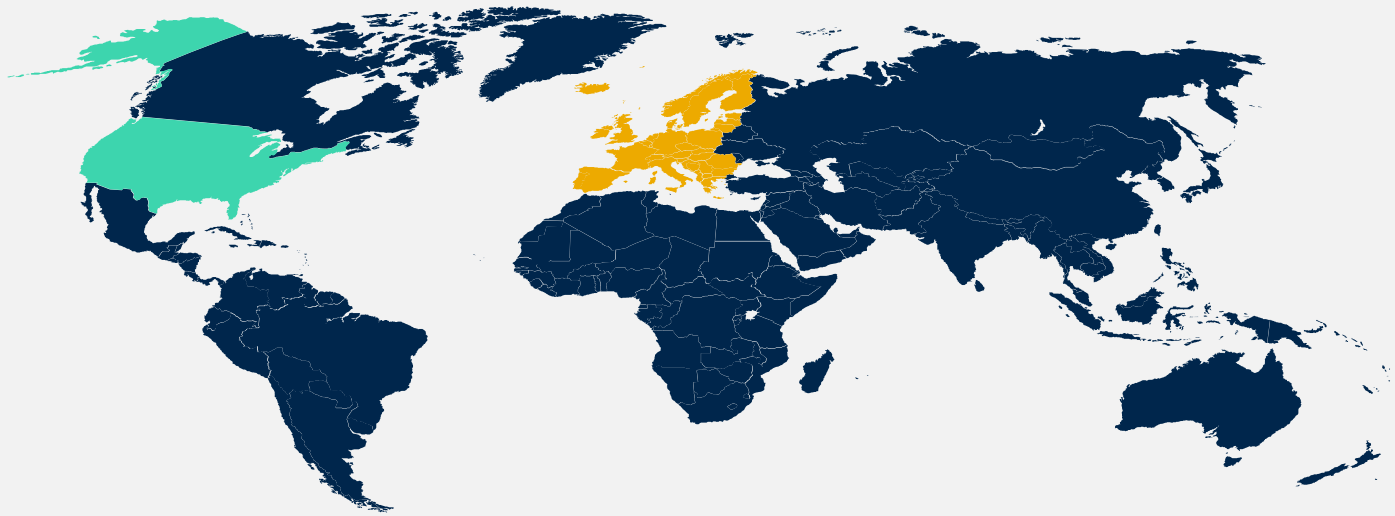
CARDIAC PHENOTYPE†
> 30% have neuropathy

WITHIN ONPATTRO® LABEL†

20K to 30K worldwide
~ 10K diagnosed‡

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

5K to 10K in EU
~ 2K diagnosed



* Based on Alnylam estimates from interviews with key opinion leaders, THAOS registry, recent clinical trials and literature

† ONPATTRO is approved in the U.S. and Canada for he polyneuropathy of hATTR amyloidosis in adults, in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy

‡ Current diagnosis rates difficult to confirm and may be lower in initial launch years

Supporting ONPATTRO® Success Globally

Alnylam Commitment to Medical and Commercial Excellence

ONPATTRO® (patisiran) can reverse polyneuropathy manifestations of the disease[1,2]

A novel RNAi-based approach that may transform the future for your patients[1-4]

At 18 months in a placebo-controlled study, ONPATTRO demonstrated:

- Reversal in neuropathy impairment from baseline as measured by modified Neuropathy Impairment Score + 7 (mNIS+7)[1]
- Improvement in quality of life from baseline as measured by Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) score[1]
- Improvement in autonomic symptoms from baseline as measured by Composite Autonomic Symptom Score 31 (COMPASS 31)[2]
- Improvement in gait speed from baseline as measured by 10-meter walk test (10MWT)[1]

Indication

ONPATTRO® (patisiran) is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Important Safety Information

Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. Monitor for signs and symptoms during infusion. Slow or interrupt the infusion if clinically indicated. Discontinue the infusion if a serious or life-threatening infusion-related reaction occurs.

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

RNA=ribonucleic acid; RNAi=RNA interference.

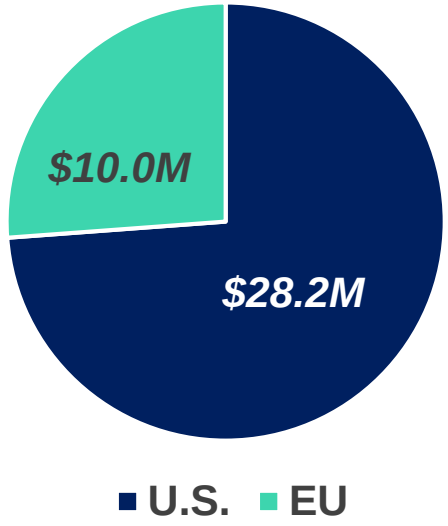
References: 1. ONPATTRO [U.S. package insert]. **2.** Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. *N Engl J Med*. 2018;379(1):11-21 **3.** Ando Y, et al. *Orphanet J Rare Dis*. 2013;8:31. **4.** Adams D, et al. *Neurology*. 2015;85(8):675-682.

ONPATTRO® Global Launch Update: Q2 2019

Strong Performance with Significant Growth Potential

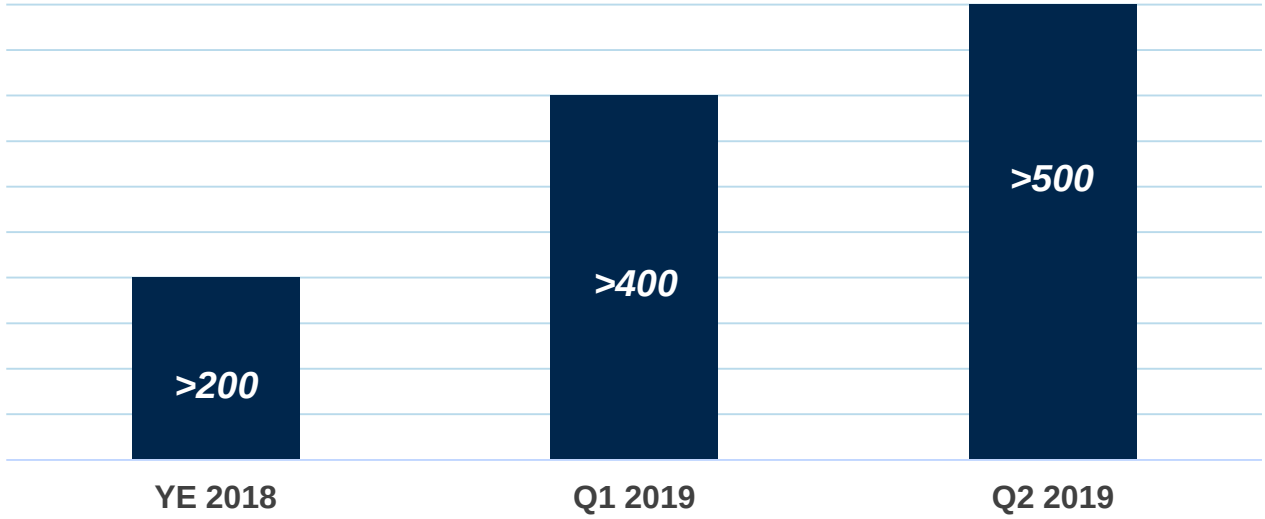
$38.2M

ONPATTRO Global Q2
Net Product Revenues



>500

Patients Worldwide on Commercial
ONPATTRO at Q2 2019



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

U.S. ONPATTRO® Demand, Prescriber Trends, and Market Access

Q2 2019 Selected Metrics

50% First-time ONPATTRO prescribers*

49% Demand from cardiologists*

28% Demand from neurologists*

23% Demand from hematologists/other*

98% U.S. lives with confirmed access to ONPATTRO, if prescribed (across commercial, Medicare, Medicaid, and other government payer categories)†

* Based on total Start Forms submitted as of end of Q2 2019. Start Forms are an incomplete picture of U.S. demand.

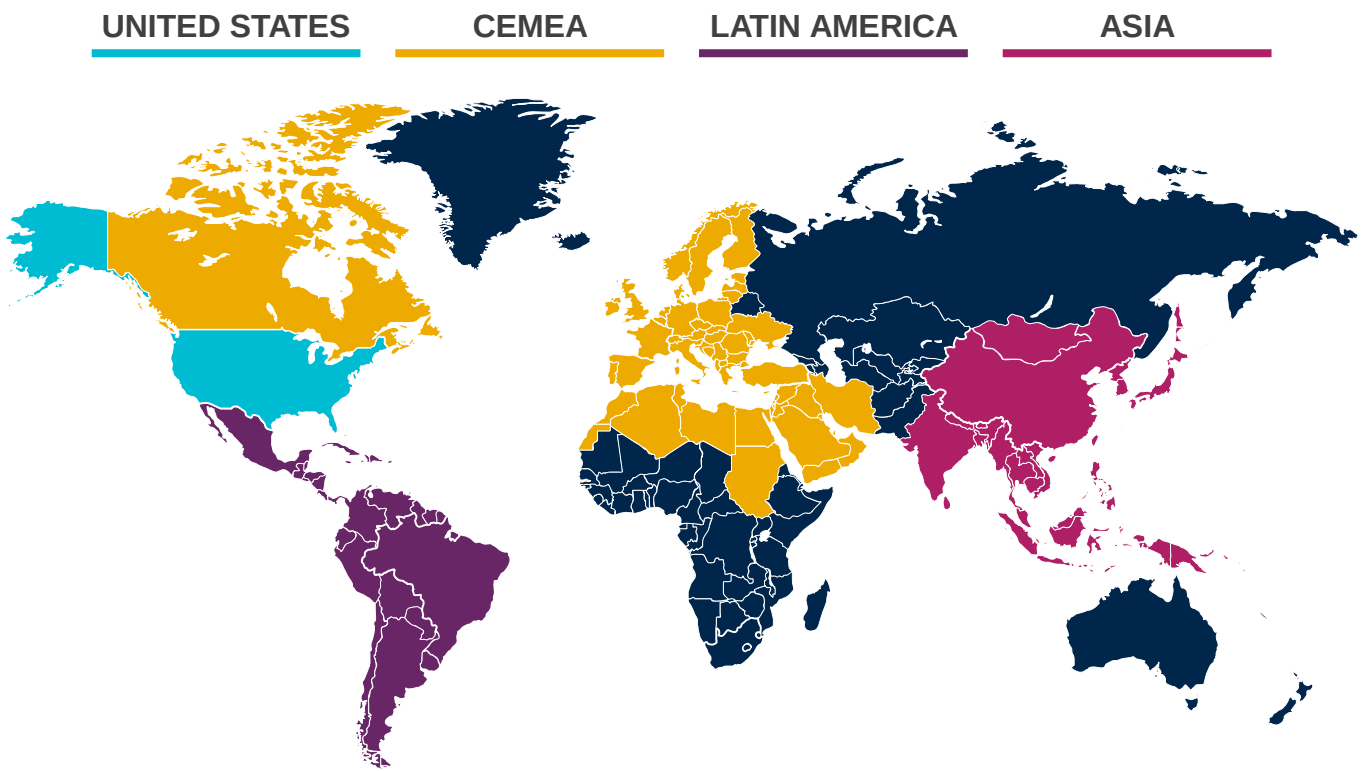
† DKP PayerScope® August 1, 2018 through June 30, 2019.

ONPATTRO® Global Commercialization

Increasing Access and Value Recognition

- Significant progress with ONPATTRO availability in CEMEA region
  - Favorable and competitively differentiating technology assessments in Germany, France, and Italy
  - Pricing agreement with NICE in England and pricing authorities in Scotland
  - Marketing authorization and commercial availability in Canada
  - Patients now have access to ONPATTRO in over 10 CEMEA countries based on direct reimbursement, named patient or reimbursed access programs

- Additional countries and regions advancing
  - Recently launched in Japan
  - Regulatory filing under review in Switzerland
  - Latin America plans progressing, starting in Brazil



CEMEA: Canada, Europe, Middle East, North Africa; EAP: Expanded Access Program.

2019 Patient Access Philosophy Report

Leveraging Innovation to Help Patients and Deliver Value

329

Patients around the world have received or are receiving ONPATTRO® via compassionate access

85%

of U.S. patients engaged in Alnylam Assist™ ask to have a visit from a Patient Education Liaison

>10

Signed Value Based Agreements (VBA)

80%

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

>15,000

Samples submitted to Alnylam Act® - a free 3rd party genetic testing and counseling program in North America

0

Price increases

355

Infusion-ready sites in U.S.

6

European countries[2] where patients have broad access to ONPATTRO, if prescribed

98%

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

Data as of Q2'19 earnings

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

[2] European Union plus European Economic Area

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

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Mike

ONPATTRO® (patisiran) Ambassador

Mike's father struggled with his health for years. By the time he was diagnosed with hATTR amyloidosis, it was already too late.

When Mike started experiencing symptoms of hATTR amyloidosis himself a few years after his father's death, he guessed what the problem was even before his official diagnosis. The pain in his hands and arms and numbness in his legs was distracting, and Mike found it difficult to focus at work or enjoy life in his forties.

When Mike heard about patisiran, he knew he wanted to try it. Now, he works with his healthcare team to make sure he receives his infusions every three weeks. He is so grateful for the time he is able to spend with his wife and children.

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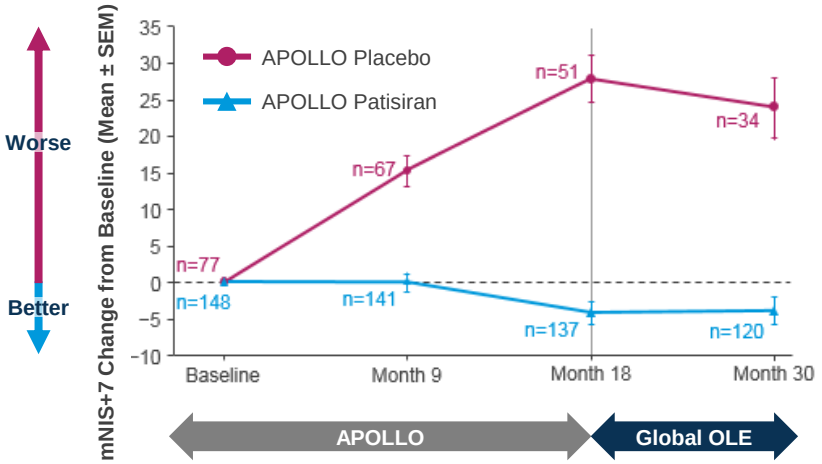
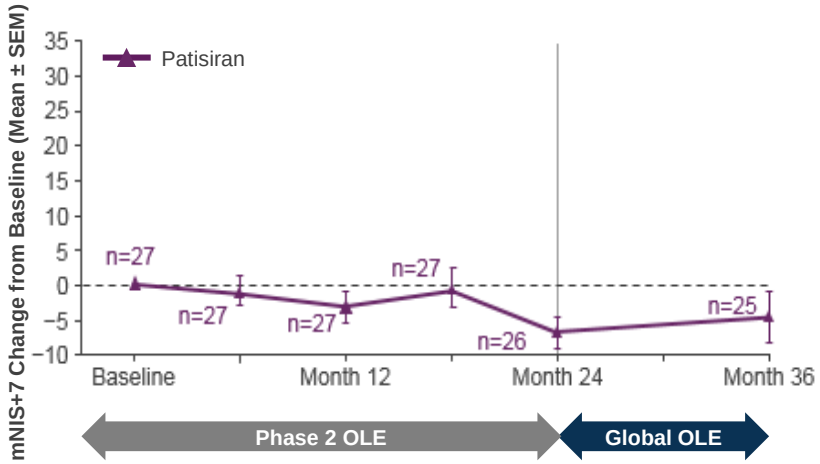
Global OLE Demonstrates Maintained Reversal of Polyneuropathy Manifestations and QOL Relative to Baseline with Consistent Safety Profile

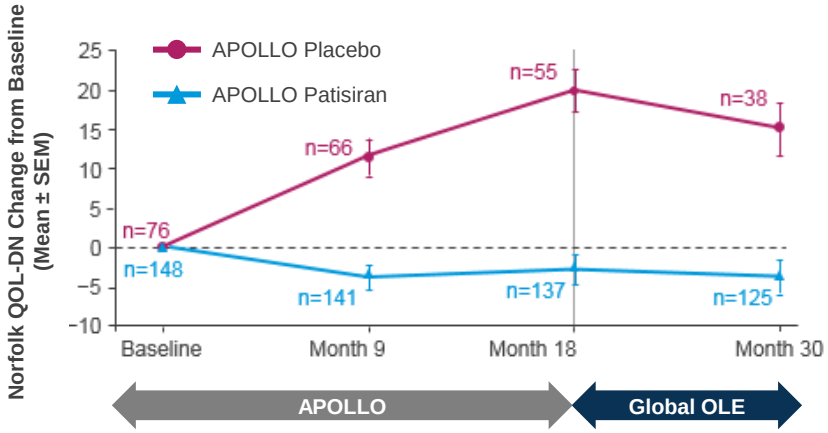
Integrated Change in mNIS+7 from APOLLO and Global OLE[a]



Integrated Change in mNIS+7 from Phase 2 OLE and Global OLE



Integrated Change in Norfolk QOL-DN from APOLLO and Global OLE



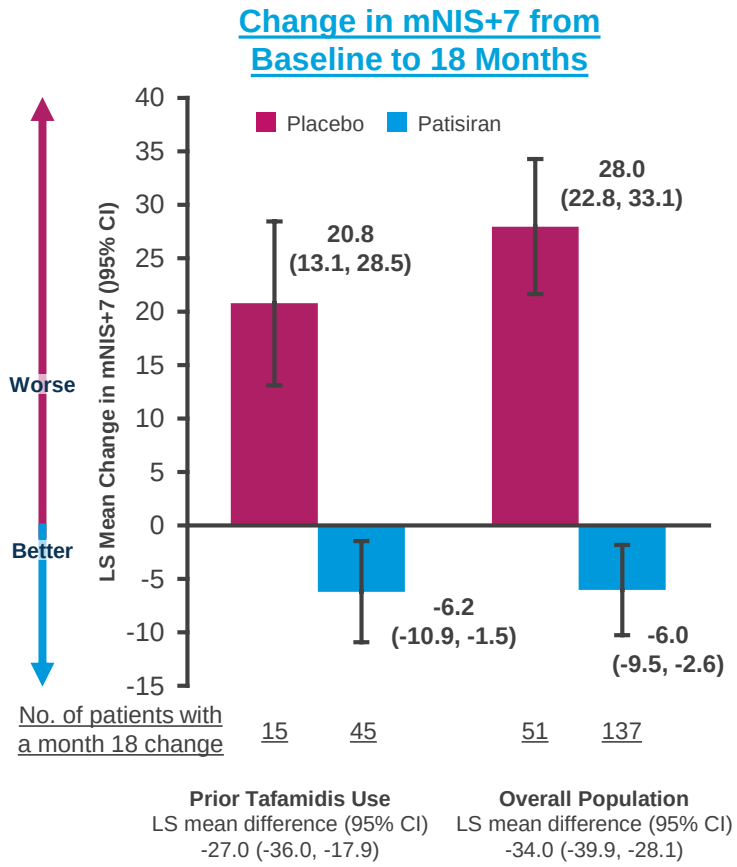
[a] For APOLLO patients initiating alternative hATTR amyloidosis treatment, mNIS+7 assessments after alternative treatment are treated as missing

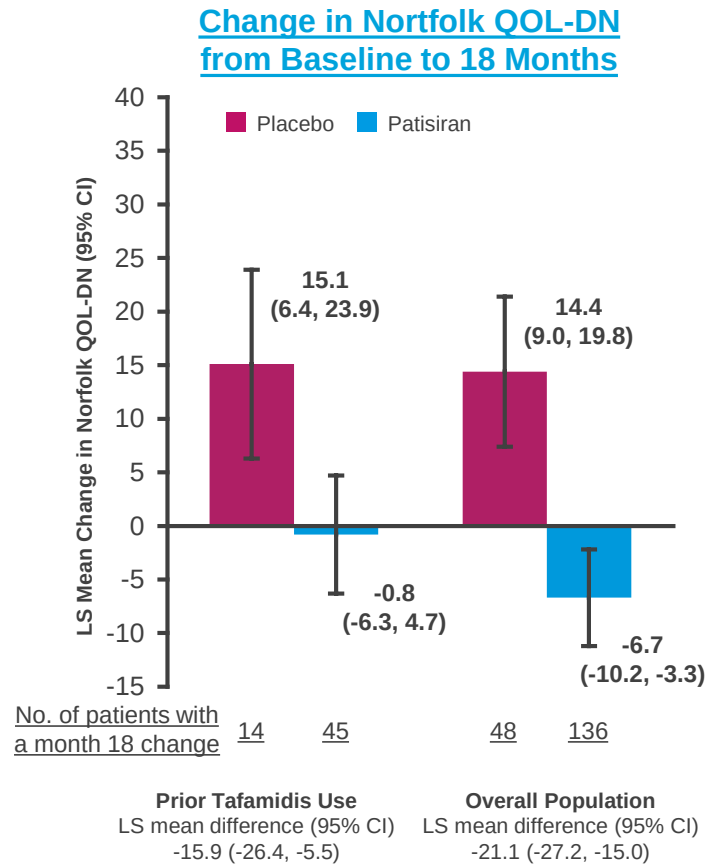
- Despite marked disease progression while receiving placebo during 18-month APOLLO study, **treatment with patisiran in previously untreated patients halted or reversed neuropathy progression and improved QOL following 12 months of patisiran treatment**
  - Delay in treatment resulted in these patients accumulating greater disease burden compared with those patients receiving patisiran during parent studies
- **Safety profile remained consistent with previous studies** and patisiran continues to show a positive benefit:risk profile

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

APOLLO Patients Previously on Tafamidis Benefited from Patisiran with Improvements in Neuropathy Impairment and Quality of Life[1]

- ~53% of APOLLO patients had prior stabilizer use
- ~33% of APOLLO patients were previously treated with tafamidis
  - 34% of patients with prior tafamidis use discontinued due to disease progression
- Patients with prior tafamidis use who received patisiran experienced clinically significant improvement from baseline in polyneuropathy and QOL compared with those who received placebo
- Safety and tolerability in prior tafamidis subgroup consistent with that seen in overall APOLLO population





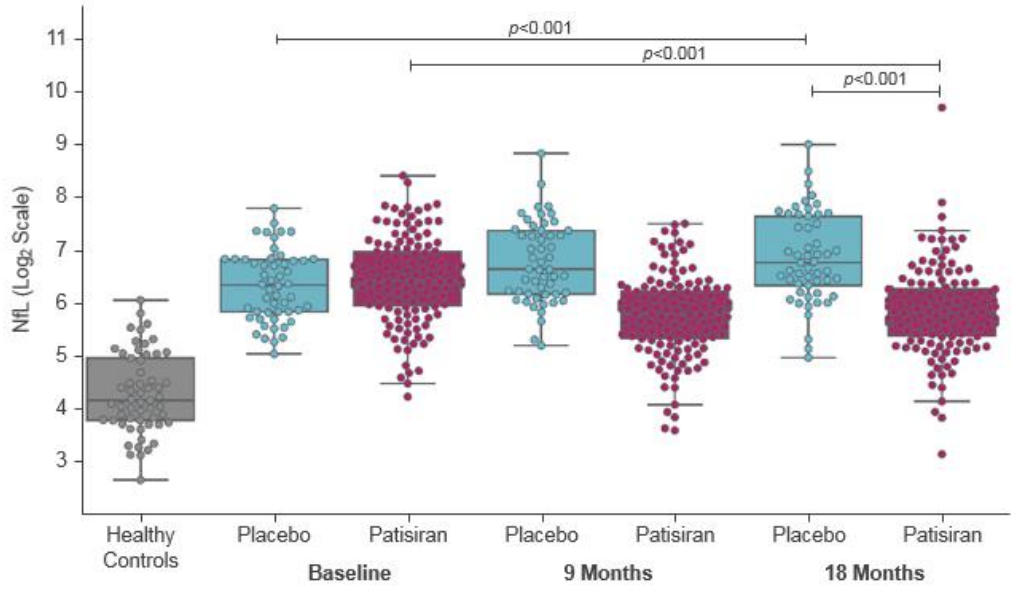
[1] Lin, PNS, June 2019. Efficacy of Patisiran in Patients with hATTR Amyloidosis and Prior Tafamidis Use: Analysis of APOLLO

New Clinical Research Findings Recently Presented

Alnylam Scientists Continue to Analyze APOLLO Data and UK Biobank

- Plasma NfL increased in hATTR amyloidosis patients, decreased with patisiran treatment in APOLLO[1]

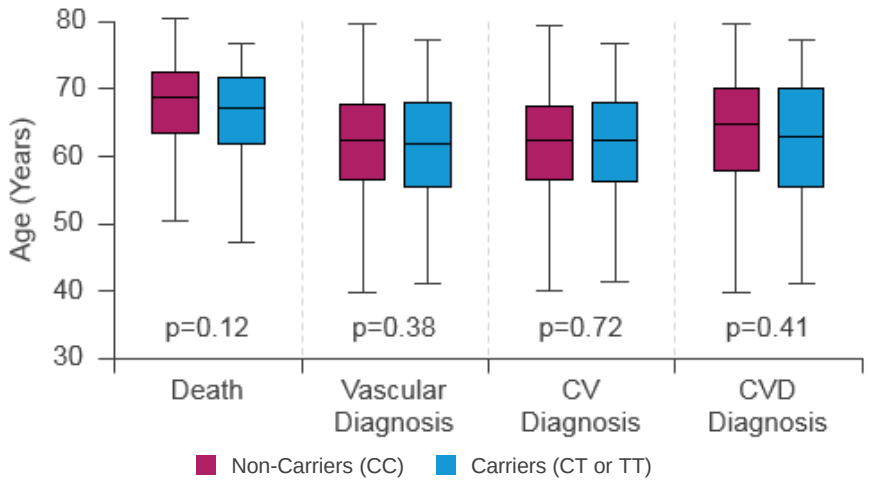
Change Over Time in NfL in Patients Treated with Placebo and Patisiran



- NfL: well-described biomarker for neuroaxonal damage; limited research on applicability in hATTR amyloidosis

- Prospective cohort study from UK Biobank: T119M mutation carriers were not found to be protected against vascular, cardiovascular, or cerebrovascular disease, or death[2]

Age at Death or Diagnosis by T119M Genotype



- In Danish cohort[3], presence of T119M mutation associated with extended lifespan, lower risk of cerebrovascular disease

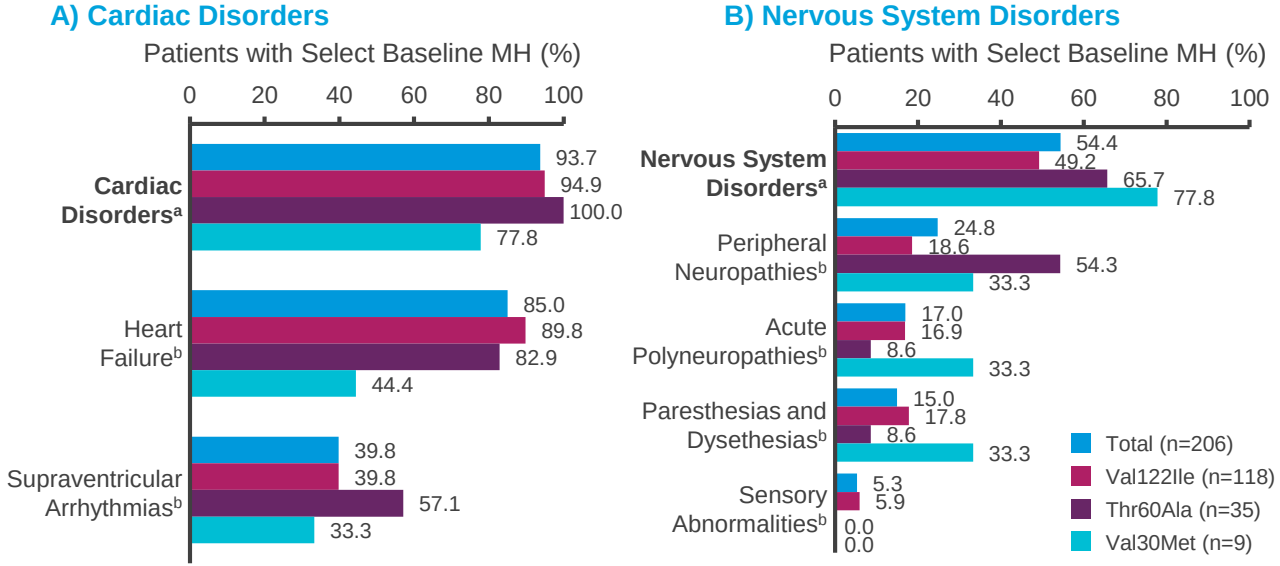
[1] Ticau, EU ATTR, Sep 2019. Neurofilament Light Chain (NfL) as a Potential Biomarker in Hereditary Transthyre in-Mediated (hATTR) Amyloidosis
[2] Parker, EU ATTR, Sep 2019. The Transthyretin Stabilizing Mutation (T119M) Is Not Associated with Extended Lifespan or Protection Against Vascular Diseases: Analysis of the UK Biobank Cohort
[3] Hornstrup et al. Arteriscler Thromb Vasc Biol 2013;33:1441–7

hATTR Amyloidosis: Multisystem Disease with Variable Genotype-Phenotype Relationship

Owing to Debilitating and Fatal Nature of Disease, Identifying Early Signs and Symptoms Crucial for Expediting Diagnosis

- In hATTR amyloidosis patients with confirmed cardiomyopathy, polyneuropathy symptoms found in ≥50% of patients[1]

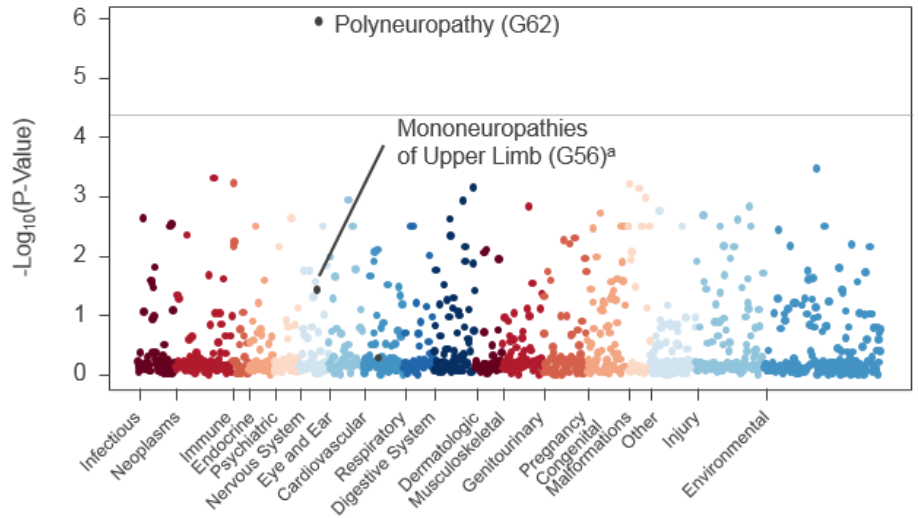
Select Baseline Medical History in Patients with hATTR Amyloidosis



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

- Carriers of V122I mutation, historically associated with predominantly cardiac phenotype, have significantly increased risk of clinical diagnosis of polyneuropathy[2]

PHEWAS Analysis of V122I Genotype Across 1,229 ICD10 Diagnosis Codes in Black Subpopulation in UK Biobank



*Mononeuropathies of the upper limb (G56) includes carpal tunnel syndrome

[1] Grogan, HFSA, Sep 2019. Identifying Mixed Phenotype: Evalua ing the Presence of Polyneuropathy in Patients wi h Hereditary Trans hyretin-Mediated Amyloidosis with Cardiomyopathy
[2] Parker, HFSA, Sep 2019. The V122I Mutation in Hereditary Transthyretin-Mediated Amyloidosis Is Significantly Associated with Polyneuropathy

Risk Factors for Mortality Identified from APOLLO and Global OLE Studies

Underscoring Importance of Earlier Clinical Suspicion of hATTR Amyloidosis to Diagnose and Treat Patients Earlier in their Disease Course

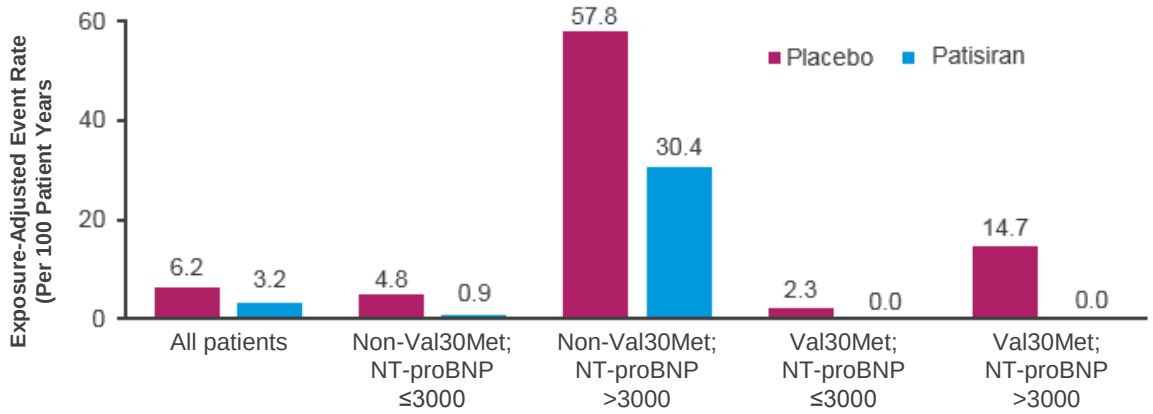
Risk Factors for Mortality

- Three most significant risk factors for mortality in patients with hATTR amyloidosis with polyneuropathy
  - Elevated NT-proBNP levels (>3000 ng/L)
  - Severity of neuropathy, and
  - Non-Val30Met genotype
- Risk factors consistent with those described in literature
- Analysis of baseline APOLLO population showed proportion of patients with both non-Val30Met and elevated NT-proBNP higher in patisiran group (11.5%) compared with placebo group (5.2%)

Integrated Analysis of Patisiran-Treated Patients: Exposure-Adjusted Mortality Rates

- Among all patisiran-treated patients, exposure-adjusted overall mortality rate per 100 patient years was 4.8
  - Estimated range for patients with ATTR amyloidosis: 6.8 – 29
- Mortality rates per 100 patient years were highest in patients from the APOLLO placebo group, whose disease had advanced during APOLLO, and lowest in patients from the Phase 2 OLE patisiran group who were treated earliest in their disease

Exposure-Adjusted Mortality Rates by Genotype and Baseline NT-proBNP Levels in APOLLO[2]



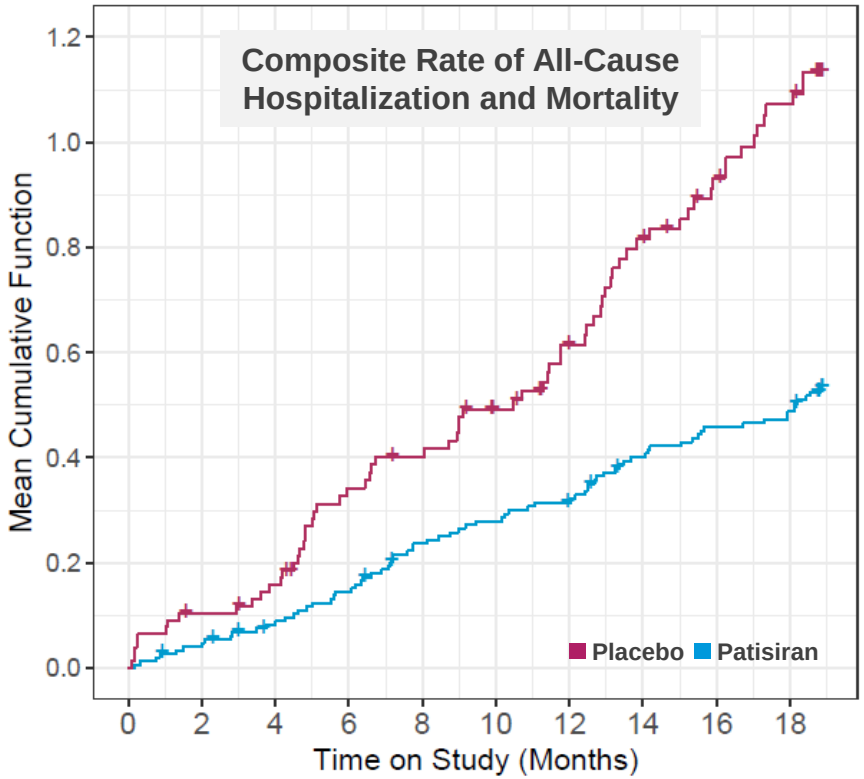
[1] Polydefkis, HFSA, Sep 2019. Risk Factors for Mortality in Patients with Hereditary Transthyre in-Mediated Amyloidosis: An Analysis of APOLLO and Global Open-Label Extension Studies

[2] Of the patients in this analysis, 12/13 had severe neuropathy (FAP 2/3) at baseline

APOLLO Phase 3 Study Results

Encouraging Evidence for Patisiran's Potential in ATTR Cardiomyopathy

~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* (n=77)	Patisiran* (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)

* For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ra io (HR) 0.48 [0.34, 0.69]
† nominal p<0.01; ‡ nominal p<0.05; Solomon S, et al. Circulation 2018

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 Indentifier: NCT03997383

APOLLO-B

Study initiated
September 2019

* Subject to protocol finalization; concomitant use of local standard of care allowed during study, including TTR stabilizer
† To reduce likelihood of infusion-related reactions, patients receive following premedica ion 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 pep ide; 6-MWD: 6-Minute Walk Distance

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Q&A Session

Cece
Living with hATTR Amyloidosis

Vutrisiran (ALN-TTRsc02)

Investigational RNAi Therapeutic

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

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

Completed Phase 1 study in healthy volunteers

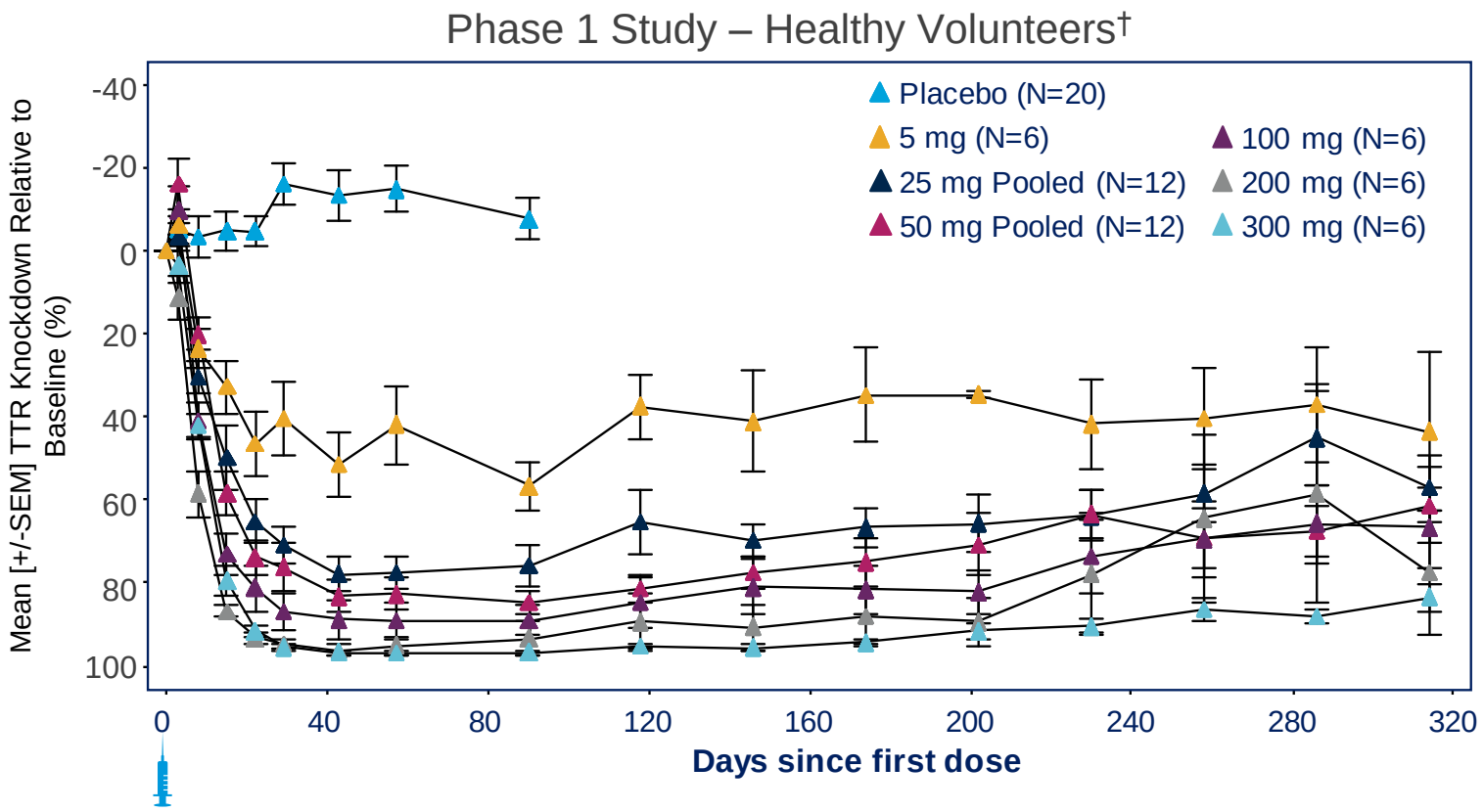
Robust Phase 3 clinical development program

- HELIOS·A study in hATTR amyloidosis now recruiting
- HELIOS·B study in ATTR amyloidosis to initiate by year-end 2019

Vutrisiran Opportunity

Advancing Continued Innovation to Patients with ATTR Amyloidosis

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



Vutrisiran

4 DOSES PER YEAR

~90% peak TTR KD predicted after repeat dosing

Safety (N=80):

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

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

Vutrisiran HELIOS·A Phase 3 Study

Randomized, Open-Label Study in Hereditary ATTR Amyloidosis Patients

ClinicalTrials.gov Indentifier: NCT03759379

HELIOS·A

Efficacy Assessments vs. APOLLO placebo arm

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

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

HELIOS-A Phase 3 study
now enrolling

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

Key Elements of HELIOS-A Study Design

Efficient, Innovative, and Patient-Centric

Patient Population

APOLLO → HELIOS-A

Patient Populations

- hATTR amyloidosis; any TTR mutation
- Neuropathy Impairment Score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

Study Structure

Statistical Analyses

Efficacy Assessments

Co-Primary Endpoints

- mNIS+7
- Norfolk QOL

Secondary Endpoints

- 10-MWT (10-meter walk test)
- mBMI
- R-ODS (activities of daily living)
- TTR KD (within-study non-inferiority, vutrisiran vs. patisiran)

- Similar Inclusion and Exclusion Criteria
- Global Footprints with Aligned Demographics
- All HELIOS-A Patients Receive Active Therapy
- Harness RNAi Mechanism and TTR KD
- Leverage Patient-Level APOLLO Data
- Comprehensive Evaluations of Disease Burden

HELIOS-B in ATTR Amyloidosis Patients with Cardiomyopathy

Leveraging a Comprehensive Body of Data Across Two Therapies and Three Studies

APOLLO

Confirmed benefit of patisiran and RNAi mechanism in patients with hATTR amyloidosis with polyneuropathy

APOLLO-B

Potential to confirm benefit and safety of patisiran in patients with ATTR amyloidosis with cardiomyopathy via a functional endpoint

HELIOS-A

Potential to confirm benefit and safety of vutrisiran in patients with hATTR amyloidosis with polyneuropathy

HELIOS-B

Potential to establish **mortality and CV hospitalization outcomes** data and **long-term treatment benefit of sustained TTR reduction** with vutrisiran in patients with ATTR amyloidosis with cardiomyopathy

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 hospitalizations (when last patient reaches Month 30)

Secondary Endpoints

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

HELIOS·B

HELIOS-B expected to initiate in **late 2019**

Study includes optional interim analysis

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Q&A Session

Alnylam's TTR Amyloidosis Franchise

Approved and Investigational Treatment Options

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

Vutrisiran

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

- Favorable efficacy and safety profile, demonstrated in APOLLO Phase 3 clinical study
- Improvement in neuropathy impairment in majority of patients
- Improvement in quality of life in majority of patients

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

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

About ONPATTRO (patisiran)

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

About Vutrisiran

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

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

Building Leading TTR Franchise to Serve Patients for Years to Come

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

Benefits of franchise

Product revenue supports continued investment and innovation in ATTR amyloidosis;

Continuous relationships with KOLs increases efficiency of clinical development;

Vutrisiran launch will utilize global footprint established with ONPATTRO

Patient and physician choice is key

Alnylam aims to provide options for patients and physicians to choose best treatment choice

ONPATTRO will remain an attractive option

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

Vutrisiran target profile

Potential to have most competitive product profile (efficacy, safety, dose/schedule) of current and emerging therapies

Ensure broad access via continued innovation with payers

TTR Franchise Strategy

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

onpattro (patisiran) lipid complex injection

APOLLO

- Established RNAi as a **new class** of medicines
- Only treatment to demonstrate **reversal of neuropathy manifestations** in majority of patients studied
- **Established safety profile**; no requirement for laboratory monitoring
- High-touch patient care with administration via **IV infusion**, q3w, with premedication

hATTR amyloidosis with polyneuropathy, including in mixed phenotype patients*

2019 – 2021

Vutrisiran HELIOS·A

- Potential for **similar efficacy** profile to ONPATTRO; also safe and well tolerated
- Potential for **certainty of sustained TTR knockdown** for 90 days after each dose
- Potential for **reduced burden of treatment**

hATTR amyloidosis with polyneuropathy, including in mixed phenotype patients†

onpattro (patisiran) lipid complex injection

APOLLO·B

- Optimizing **known asset** with established safety profile
- Building on exploratory cardiac data (APOLLO) for **rapid expansion** of patient population with 6-MWT data

ATTR amyloidosis with cardiomyopathy‡

2021 – 2023

Vutrisiran HELIOS·B

- Longer-term investment, with potential for high-impact cardiac **outcomes data** (death and cardiovascular hospitalizations)
- Potential for **most compelling data package**
- Potential for **most competitive product profile**
- Potential to **achieve and sustain market-leading position**

ATTR amyloidosis with cardiomyopathy†

2023 & Beyond

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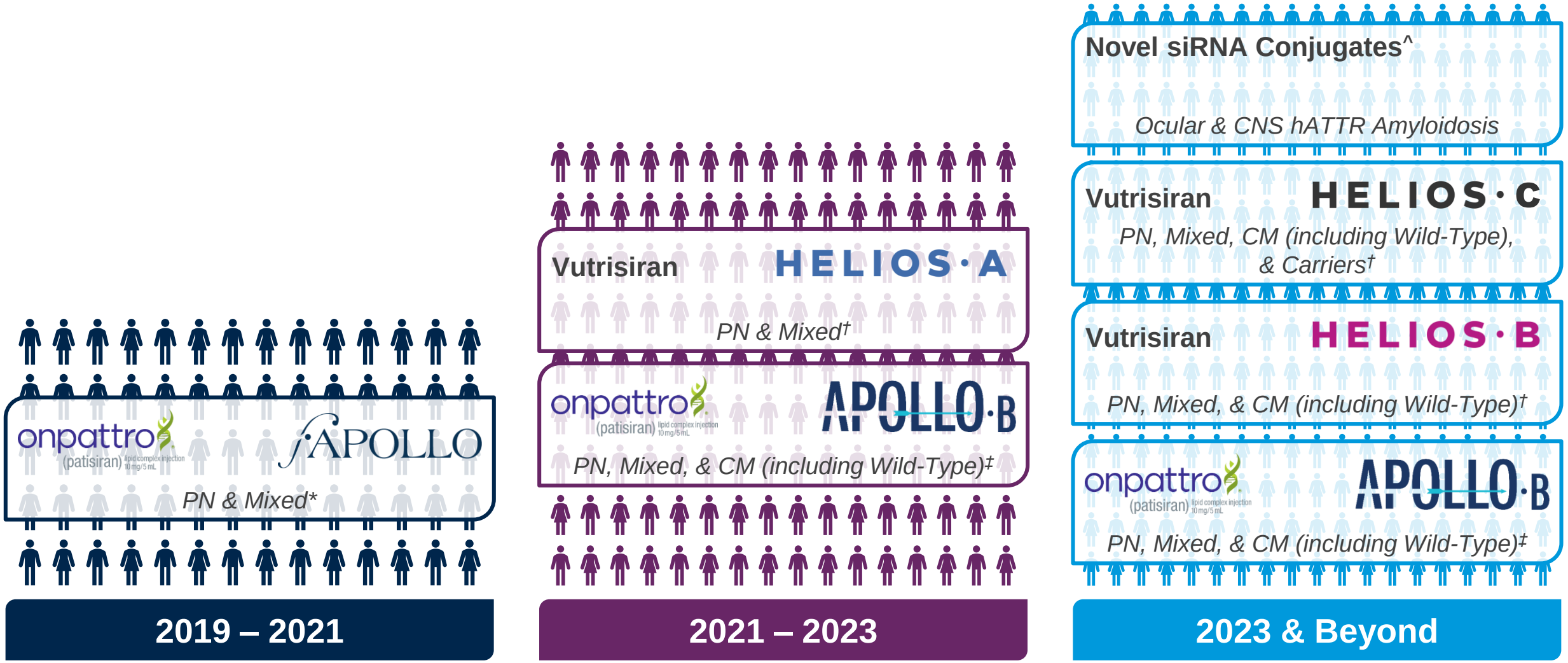
Alnylam ATTR Amyloidosis Franchise

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



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

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

Alnylam's Commitment: Putting Patients First

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Upcoming RNAi Roundtables

Givosiran, in Development for the Treatment of Acute Hepatic Porphyria

- Monday, October 7, 2019 – 9:30 am ET

Lumasiran, in Development for the Treatment of Primary Hyperoxaluria Type 1

- Thursday, October 10, 2019 – 11:30 am ET

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company's website, www.alnylam.com/capella

SAVE THE DATE

Alnylam R&D Day

Friday, November 22, 2019

Westin Times Square

New York City

Alnylam® PHARMACEUTICALS

CHALLENGE ACCEPTED

Alnylam PHARMACEUTICALS