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

RNAi ROUNDTABLE 2021

July 16, 2021

Alnylam® PHARMACEUTICALS

Agenda

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

Introduction and Overview of ATTR Amyloidosis
- Rena Denoncourt – Vice President, ATTR Amyloidosis Franchise Lead
- Patient Story – Dawn, caregiver and hATTR amyloidosis patient

Recent Vutrisiran Clinical Data in Patients with hATTR Amyloidosis with Polyneuropathy
- Rebecca Shilling, M.D. – Director, Clinical Research

Recent Patisiran Clinical Data in Post-OLT Patients and Update on Phase IV Study
- Patrick Jay, M.D. – Director, Clinical Research

KOL Perspective on ATTR Amyloidosis
- Mat Maurer, M.D. – Columbia University Medical Center, Arnold and Arlene Goldstein Professor of Cardiology

RNAi Therapeutics in Development for ATTR Amyloidosis with Cardiomyopathy
- John Vest, M.D. – Vice President, Clinical Research

Alnylam's ATTR Amyloidosis Franchise Opportunity
- Rena Denoncourt – Vice President, ATTR Amyloidosis Franchise Lead

Q&A Session

Reminders

Event will run for approximately 60 - 75 minutes

Q&A session at end of presentation

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

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

Alnylam Forward Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, including expectations regarding our aspiration to become a leading biotech company, and the planned achievement of our “Alnylam P5x25” strategy, plans for additional global regulatory filings and the continuing product launches of our approved products, the current or potential therapy options for ATTR amyloidosis, the potential expansion of the ATTR amyloidosis franchise, the safety and efficacy of vutrisiran based upon the 9-month data from the Phase 3 HELIOS-A study, vutrisiran and its potential as an attractive new treatment option for hATTR amyloidosis patients with polyneuropathy with subcutaneous administration and quarterly dosing, results from a Phase 3b open-label study of patisiran and the potential benefit of patisiran treatment for patients with polyneuropathy progression after receiving an OLT, the Phase IV observational study of patisiran, the achievement of additional pipeline and regulatory milestones for vutrisiran and patisiran, including in the HELIOS-B and APOLLO-B studies, the evidence for investigational RNAi therapeutics in ATTR cardiomyopathy, and the key drivers of potential market expansion with vutrisiran. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the “Risk Factors” filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

This presentation is not intended to convey conclusions about efficacy or safety as to any investigational uses or dosing regimens of any products or investigational RNAi therapeutics. There is no guarantee that any investigational therapeutics or dosing regimens for such therapeutics will successfully complete clinical development or gain health authority approval.

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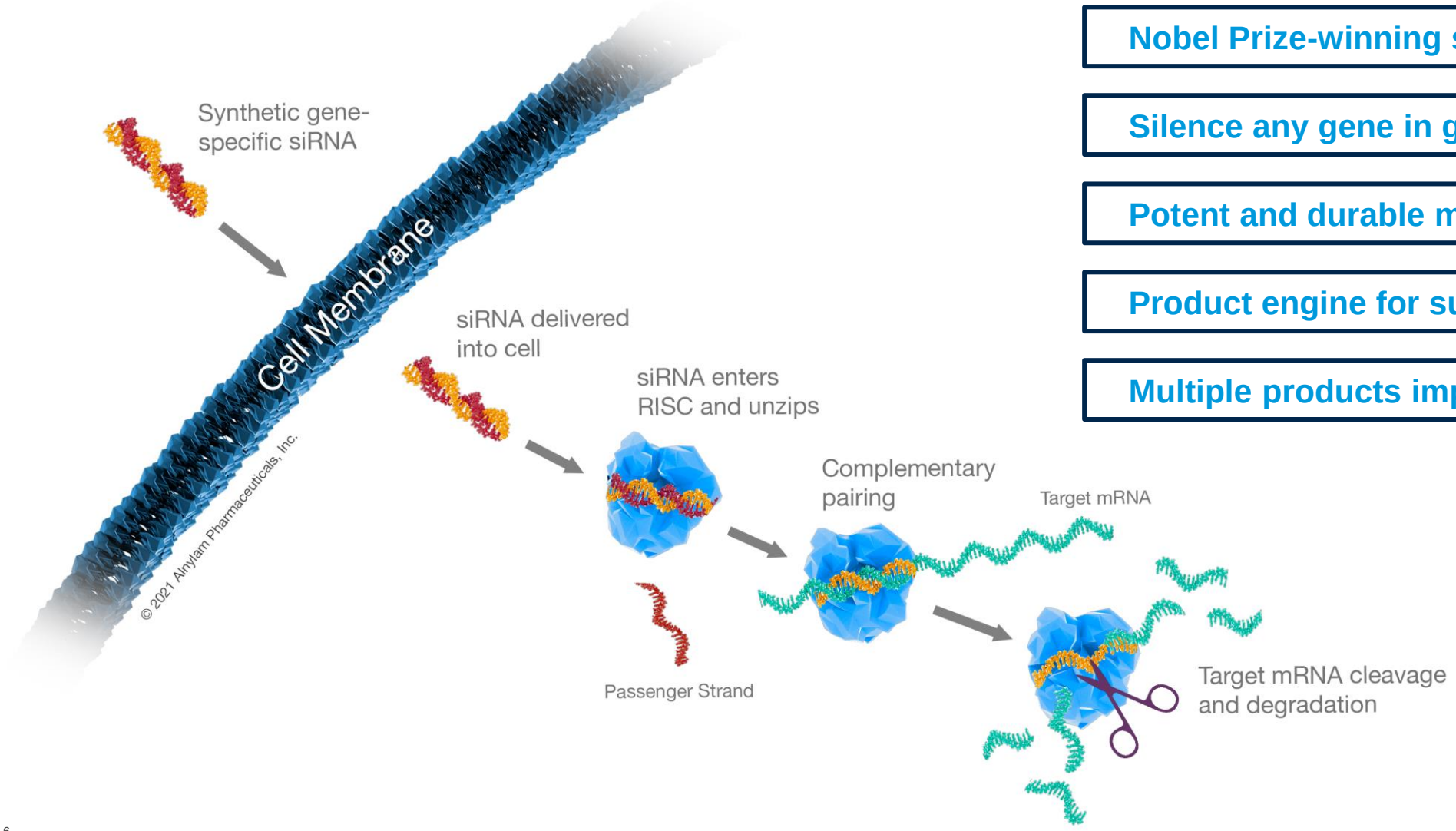
RNAi Therapeutics: New Class of Innovative Medicines

Clinically and Commercially Established Approach with Transformational Potential



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

Alnylam P5x25

Patients: Over 0.5 million on Alnylam RNAi therapeutics globally

Products: 6+ marketed products in rare and prevalent diseases

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

Performance: ≥40% revenue CAGR through YE 2025

Profitability: Achieve sustainable non-GAAP profitability within period

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

Compelling Commercial Profile of Existing and Emerging Medicines

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

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

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

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

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

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

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

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

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

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

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

As of July 2021

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

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Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran*	*ATTR Amyloidosis*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Renal Stones*	●	●		Global
Cemdisiran*	*Complement-Mediated Diseases*	●			50-50
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As of July 2021

Cece
Diagnosed with hATTR amyloidosis (USA)

ATTR Amyloidosis

Rare, Progressively Debilitating, and 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

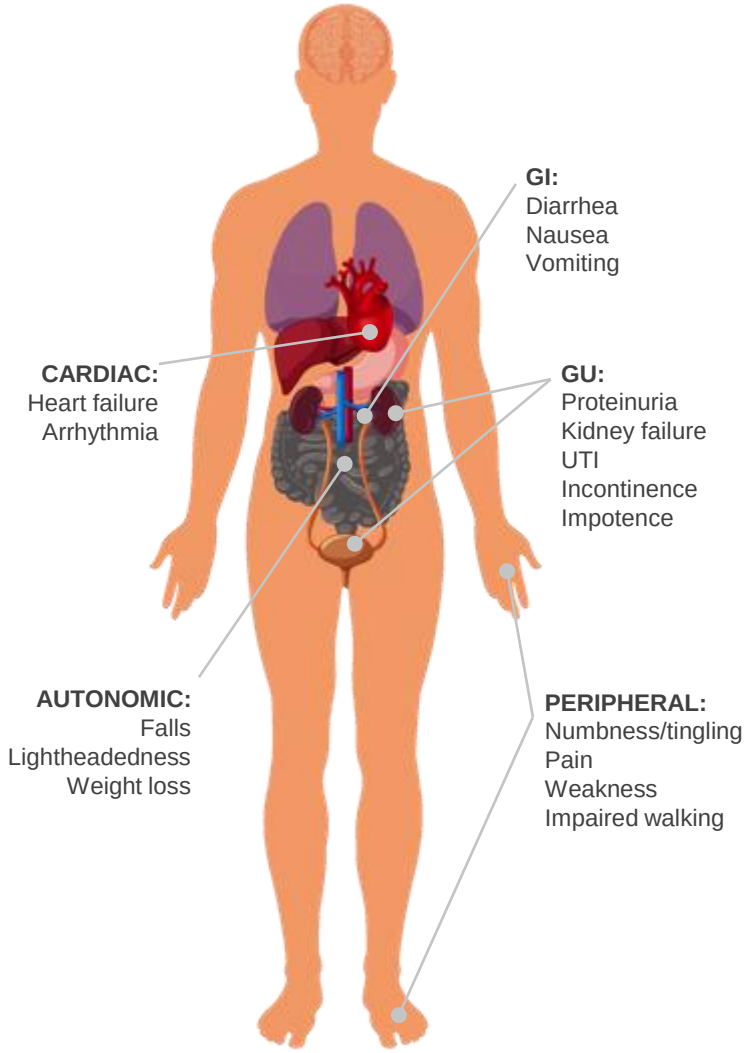
~50,000

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 (includes hATTR amyloidosis patients with polyneuropathy and cardiomyopathy)

A Patient Story

Diagnosed with hATTR Amyloidosis with Polyneuropathy

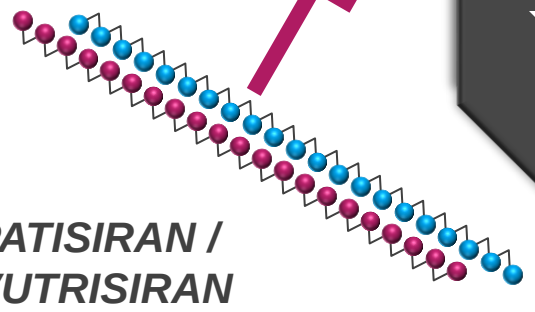
Dawn

Caregiver and Patient

“With therapies now available, and more in clinical development, the trauma of chronic illness and loss ends with me, and my family and I can be hopeful for the future.”

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 mutant and wild-type TTR

Production of mutant and wild-type TTR in liver*

Reduce circulating TTR

Prevent or clear tissue amyloid deposits

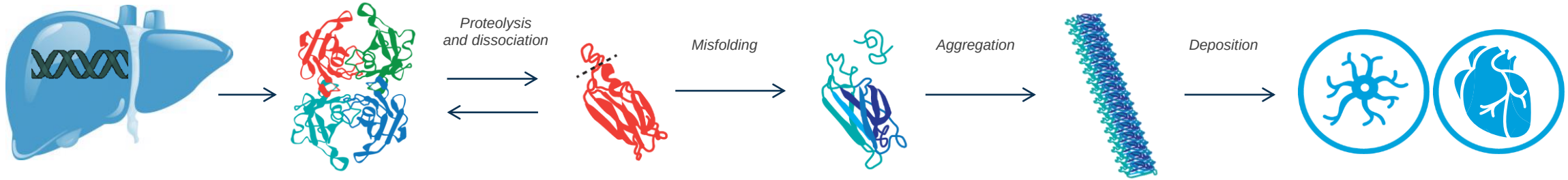
Halt or improve progressive manifestations of disease

* >95% of TTR in circulation produced in liver

Current or Potential Therapy Options for ATTR Amyloidosis

RNAi Therapeutics Work by Silencing the Source of Disease

ATTR Amyloidosis Disease Cascade and Current/Potential Therapies



Eliminate production of mutant TTR:
- Orthotopic liver transplant

Suppression of TTR synthesis (gene silencing):
- **RNAi (patisiran, vutrisiran)**
- Antisense oligonucleotides
- Gene editing

Prevent dissociation of TTR tetramer:
- TTR stabilizers

Remove existing amyloid:
- Monoclonal antibodies

Alnylam's ATTR Amyloidosis Franchise

Approved Treatment Option, Investigational Clinical Programs, and a Preclinical Development Program

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

An Approved RNAi Therapeutic for Treatment of Polyneuropathy of hATTR Amyloidosis*

About ONPATTRO

- Favorable efficacy and safety profile in APOLLO
- APOLLO-B ongoing to evaluate patisiran in ATTR amyloidosis with cardiomyopathy ‡
- IV administration, once every 3 weeks

Vutrisiran

An Investigational RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis†

About Vutrisiran

- Positive efficacy results and acceptable safety profile in HELIOS-A in hATTR amyloidosis with polyneuropathy
- HELIOS-B ongoing in ATTR amyloidosis with cardiomyopathy
- Subcutaneous administration, once every 3 months with potential for biannual dosing regimen

ALN-TTRsc04

A Preclinical RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis

About ALN-TTRsc04

- IKARIA platform
- IND expected in 2022
- Subcutaneous administration with potential annual dosing regimen and >90% serum TTR reduction
- No third-party royalties; exclusivity expected to extend beyond 2040

* 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; see Full Prescribing Information ‡ 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

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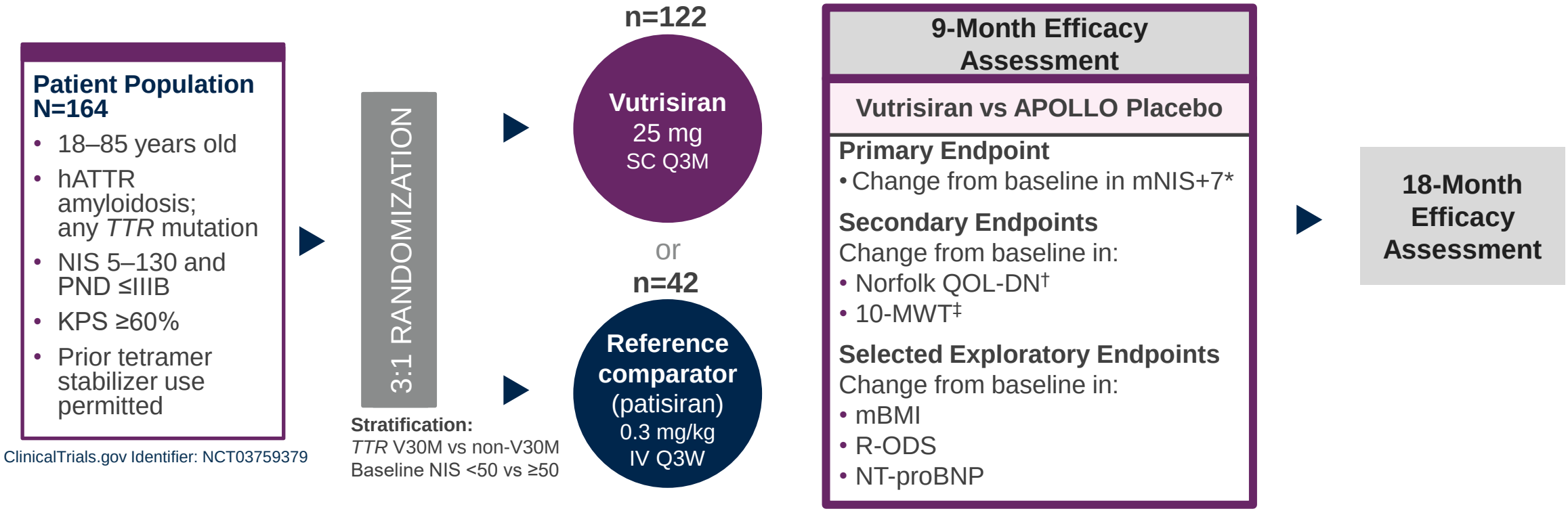
Vutrisiran Phase 3 HELIOS·A Study

Randomized, Open-label Study in Patients with hATTR Amyloidosis with Polyneuropathy

- Presenting 9-month primary efficacy analysis compared with the external placebo group (placebo arm of APOLLO) selected on the basis of similar patient populations and endpoints



*Higher scores of mNIS+7 indicate more neuropathy impairment (range, 0 to 304). †Higher scores of Norfolk QOL-DN indicate worse quality of life (range, −4 to 136). ‡10-MWT speed (m/s) = 10 meters/mean time (seconds) taken to complete two assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function.
10-MWT, 10-meter walk test; IV, intravenous; KPS, Karnofsky performance status; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro-brain natriuretic peptide; PND, polyneuropathy disability;
Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; TTR, transthyretin.

Adams et al., AAN, April 2021

Baseline Demographic and Disease Characteristics

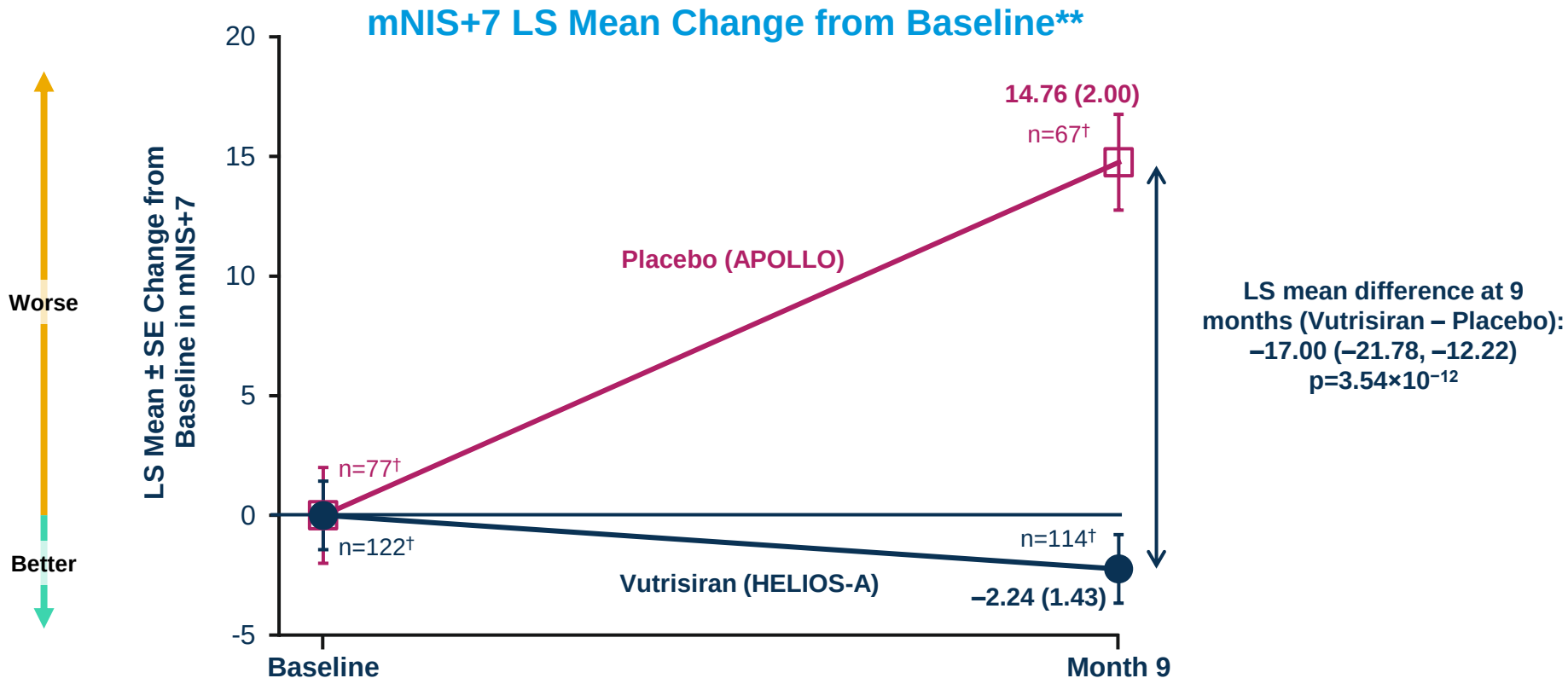
Characteristic	APOLLO	HELIOS-A	
	Placebo n=77	Vutrisiran n=122	Patisiran n=42
Age (years), median (range)	63 (34, 80)	60 (26, 85)	60 (31, 81)
Males, n (%)	58 (75)	79 (65)	27 (64)
TTR genotype, n (%)			
V30M	40 (52)	54 (44)	20 (48)
Non-V30M	37 (48)	68 (56)	22 (52)
NIS, mean (range)	57 (7, 126)	43 (5, 127)	43 (6, 116)
PND score,* n (%)			
I: preserved walking, sensory disturbances	20 (26)	44 (36)	15 (36)
II: impaired walking but can walk without stick or crutch	23 (30)	50 (41)	17 (40)
IIIA: walk with 1 stick or crutch	22 (29)	16 (13)	7 (17)
IIIB: walk with 2 sticks or crutches	11 (14)	12 (10)	3 (7)
Cardiac subpopulation, n (%)†	36 (47)	35 (29)	13 (31)

*One patient (1.3%) in external placebo group had a PND score of IV defined as confined to wheelchair or bedridden (not shown on the slide). †Cardiac subpopulation was defined as patients who had pre-existing evidence of cardiac amyloid involvement (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history).
NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; TTR, transthyretin.

Adams et al., AAN, April 2021

Significant Improvement in Neuropathy Impairment with Vutrisiran

- Vutrisiran achieved statistically significant improvement in mNIS+7 at 9 months, compared with the external placebo group
  - Improvements across all pre-specified patient subgroups* and components of mNIS+7 (data not shown)

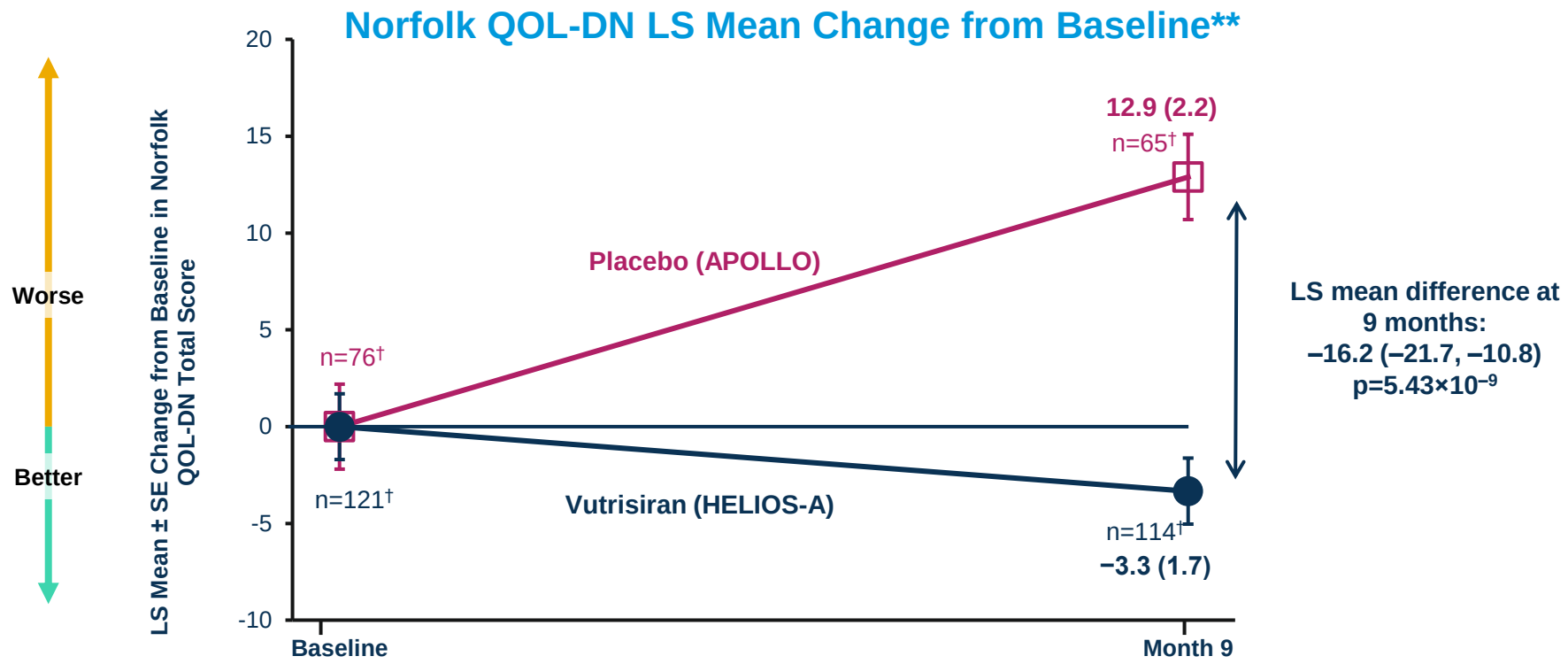


*Pre-specified patient subgroups included age (<65 or ≥65), sex, race, region, baseline NIS (<50 or ≥50), previous tetramer stabilizer use, genotype (V30M or non-V30M), FAP stage (I or II and III), cardiac subpopulation (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history),

mITT population (all randomized patients who received any amount of study drug). **At baseline, the mean (±SD) mNIS+7 was 60.6 (36.0) in the vutrisiran group and 74.6 (37.0) in external placebo group.
†Number of evaluable patients.
LS, least squares; mITT, modified intent-to-treat; mNIS+7, modified Neuropathy Impairment Score +7; SD, standard deviation; SE, standard error.
Adams et al., AAN, April 2021

Significant Improvement in Quality of Life with Vutrisiran

- Vutrisiran achieved statistically significant improvement in Norfolk QOL-DN at 9 months, compared with the external placebo group
  - Improvements across all pre-specified patient subgroups* and domains of Norfolk QOL-DN (data not shown)



*Pre-specified patient subgroups included age (<65 or ≥65), sex, race, region, baseline NIS (<50 or ≥50), previous tetramer stabilizer use, genotype (V30M or non-V30M), FAP stage (I or II and III), cardiac subpopulation (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history)

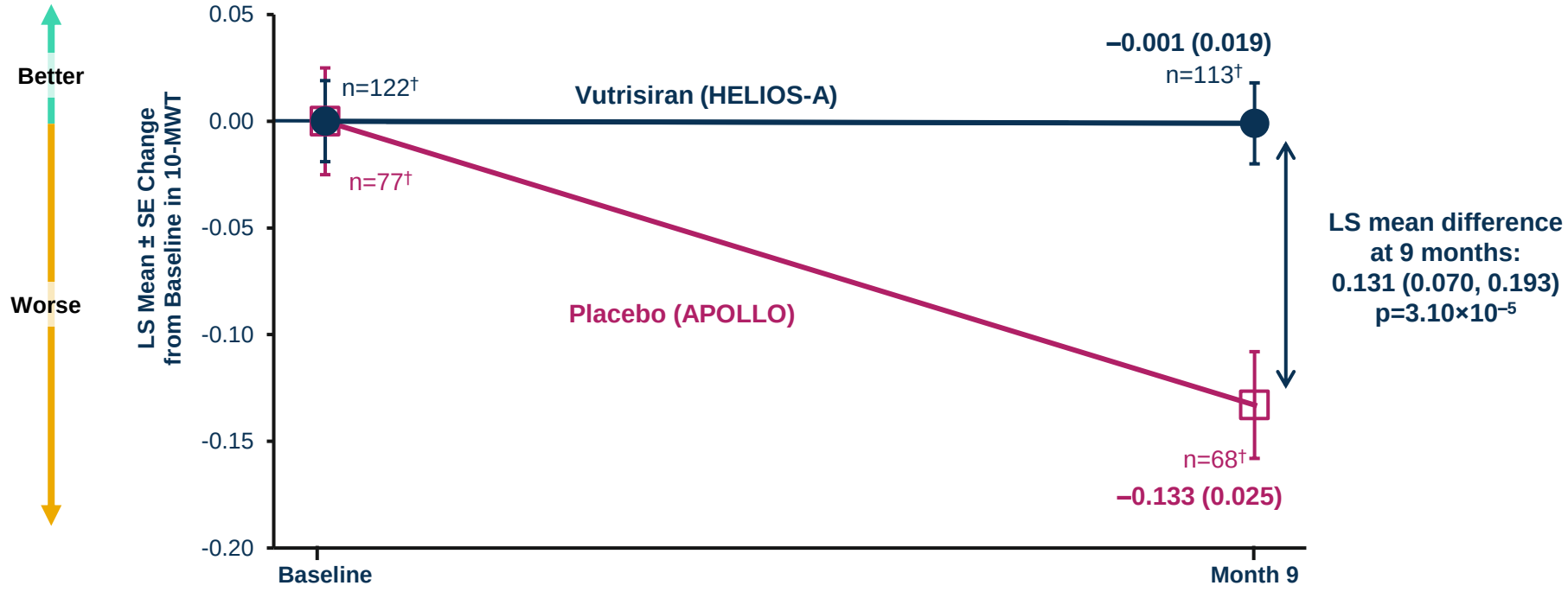
mITT population. **At baseline, the mean (±SD) Norfolk QOL-DN score was 47.1 (26.3) in the vutrisiran group and 55.5 (24.3) in the external placebo group. †Number of evaluable patients.
10-MWT, 10-meter walk test; LS, least squares; mBMI, modified body mass index; mITT, modified intent-to-treat; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro-brain natriuretic peptide; QOL, quality of life; R-ODS, Rasch-built overall disability scale; SD, standard deviation; SE, standard error.

Adams et al., AAN, April 2021

Significant Improvement in Gait Speed with Vutrisiran

- Vutrisiran achieved statistically significant improvement in gait speed measured by 10-MWT at 9 months, compared with the external placebo group

10-MWT LS Mean Change from Baseline*



*mITT population. **At baseline, the mean (±SD) 10-MWT was 1.006 (0.393) in the vutrisiran group and 0.790 (0.319) in the external placebo group**. †Number of evaluable patients.
10-MWT, 10-meter walk test; LS, least squares; mBMI, modified body mass index; mITT, modified intent-to-treat; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro-brain natriuretic peptide; QOL, quality of life; R-ODS, Rasch-built overall disability scale; SD, standard deviation; SE, standard error.

Adams et al., AAN, April 2021

Treatment Effects Observed in Vutrisiran Were Consistent With Patisiran in APOLLO

Post Hoc Cross-Study Assessment of LS Mean Change From Baseline to 9 Months for Endpoints for Vutrisiran and APOLLO Patisiran Arm

Endpoint	HELIOS-A		APOLLO	
	Vutrisiran (n=122) LS mean change from baseline (95% CI)	Vutrisiran – Placebo LS mean difference (95% CI)	Patisiran (n=148) LS mean change from baseline (95% CI)	Patisiran – Placebo LS mean difference (95% CI)
mNIS+7*	–2.2 (–5.0, 0.6)	–17.0 (–21.8, –12.2)	–2.0 (–5.0, 0.9)	–16.0 (–20.7, –11.3)
Norfolk QOL-DN†	–3.3 (–6.6, –0.1)	–16.2 (–21.7, –10.8)	–7.5 (–10.5, –4.6)	–15.0 (–19.8, –10.2)
10-MWT‡ (m/s)	–0.001 (–0.038, 0.036)	0.131 (0.070, 0.193)	0.05 (0.013, 0.086)	0.156 (0.099, 0.213)

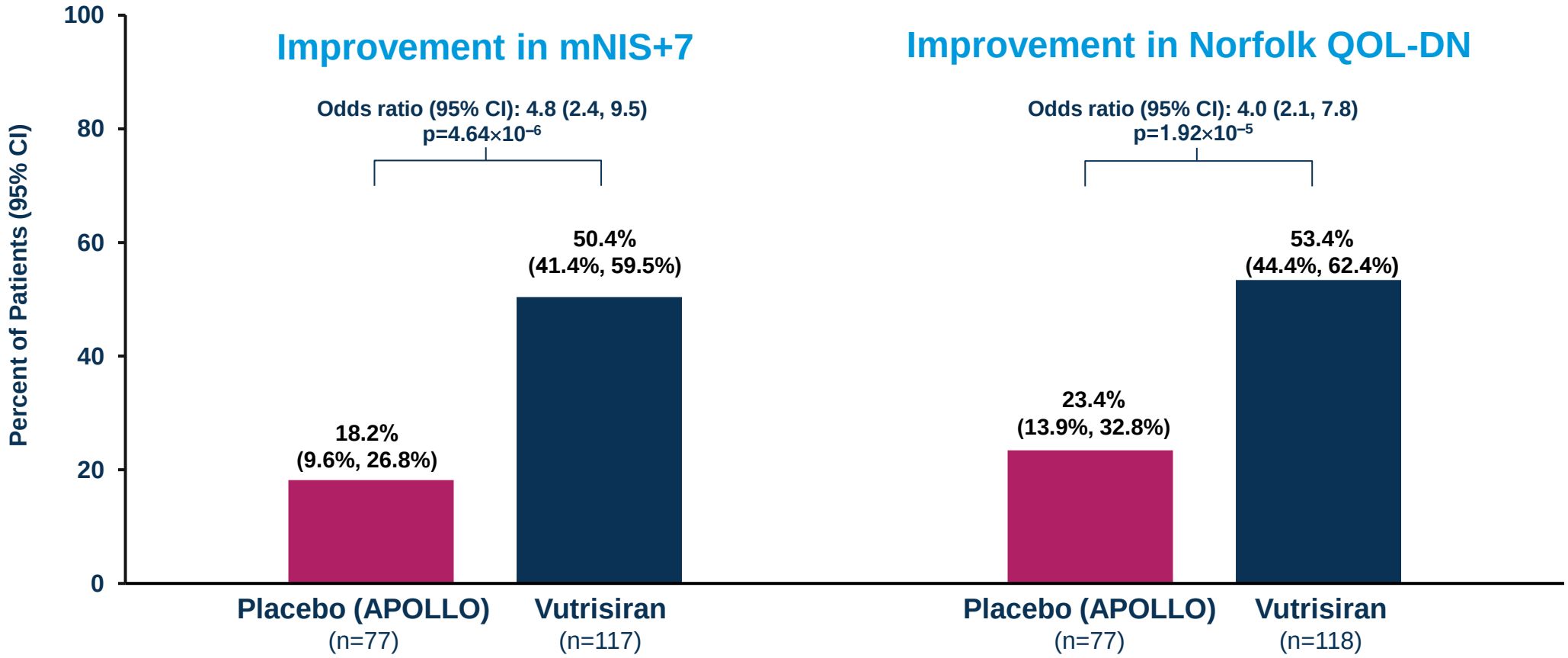
- Vutrisiran efficacy in HELIOS-A similar to that seen with patisiran in APOLLO study
- Patisiran efficacy in HELIOS-A similar to that previously observed in APOLLO study
  - Mean change from baseline for the HELIOS-A patisiran arm was –1.41 for mNIS+7, 0.1 for Norfolk and –0.039 m/s for 10-MWT
    - HELIOS-A patisiran arm not intended for statistical testing vs vutrisiran for mNIS+7, Norfolk QOL-DN, or 10-MWT endpoints; results presented as arithmetic means per statistical analysis plan

*Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304). †Higher scores of Norfolk QOL-DN indicate worse quality of life (range, -4 to 136). ‡10-meter walk test (10-MWT) speed (m/s) = 10 meters/mean time (seconds) taken to complete two assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function.
10-MWT, 10-meter walk test; LS, least squares; mITT, modified intent-to-treat; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built overall disability scale.

Adams et al., PNS, June 2021

Improvement in Neurologic Impairment and Quality of Life in Majority of Patients Receiving Vutrisiran

Percent of Patients Achieving Improvement in mNIS+7* and Norfolk QOL-DN* at Month 9



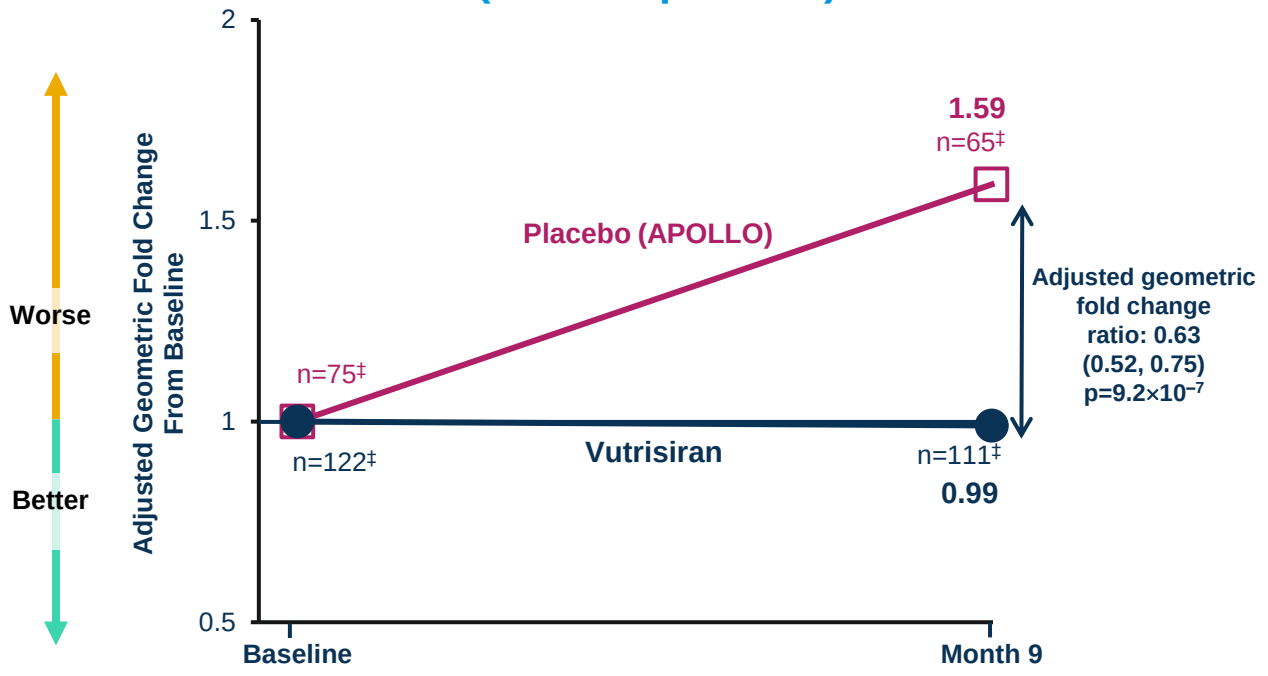
Improvement defined as patients with <0-point increase from baseline to 9 months. *Patients with missing postbaseline values due to COVID-19 (including values on or after onset of a serious COVID-19 AE) were excluded from analysis. Assessments after initiation of local standard treatment for hATTR amyloidosis were treated as missing.

AE, adverse event; CI, confidence interval; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy.

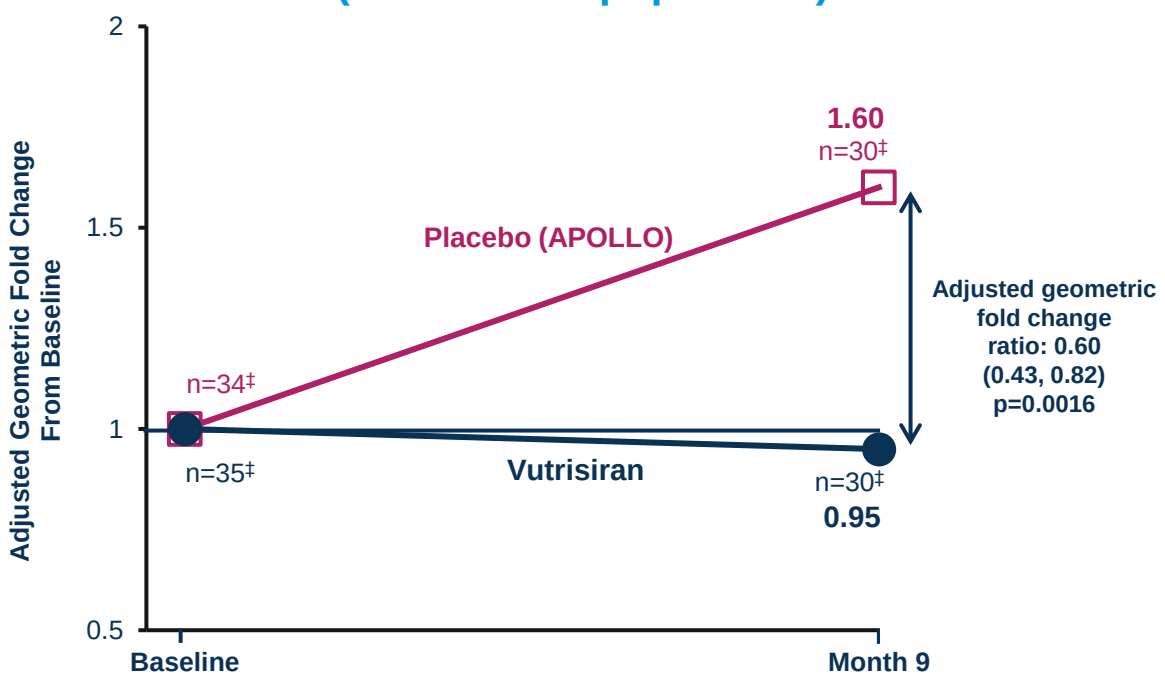
Adams et al., PNS, June 2021

Exploratory Endpoints at 9 months, Including NT-proBNP, Demonstrated Improvements Compared with the External Placebo Group

Change from Baseline in NT-proBNP (mITT Population)*



Change from Baseline in NT-proBNP (Cardiac Subpopulation)†

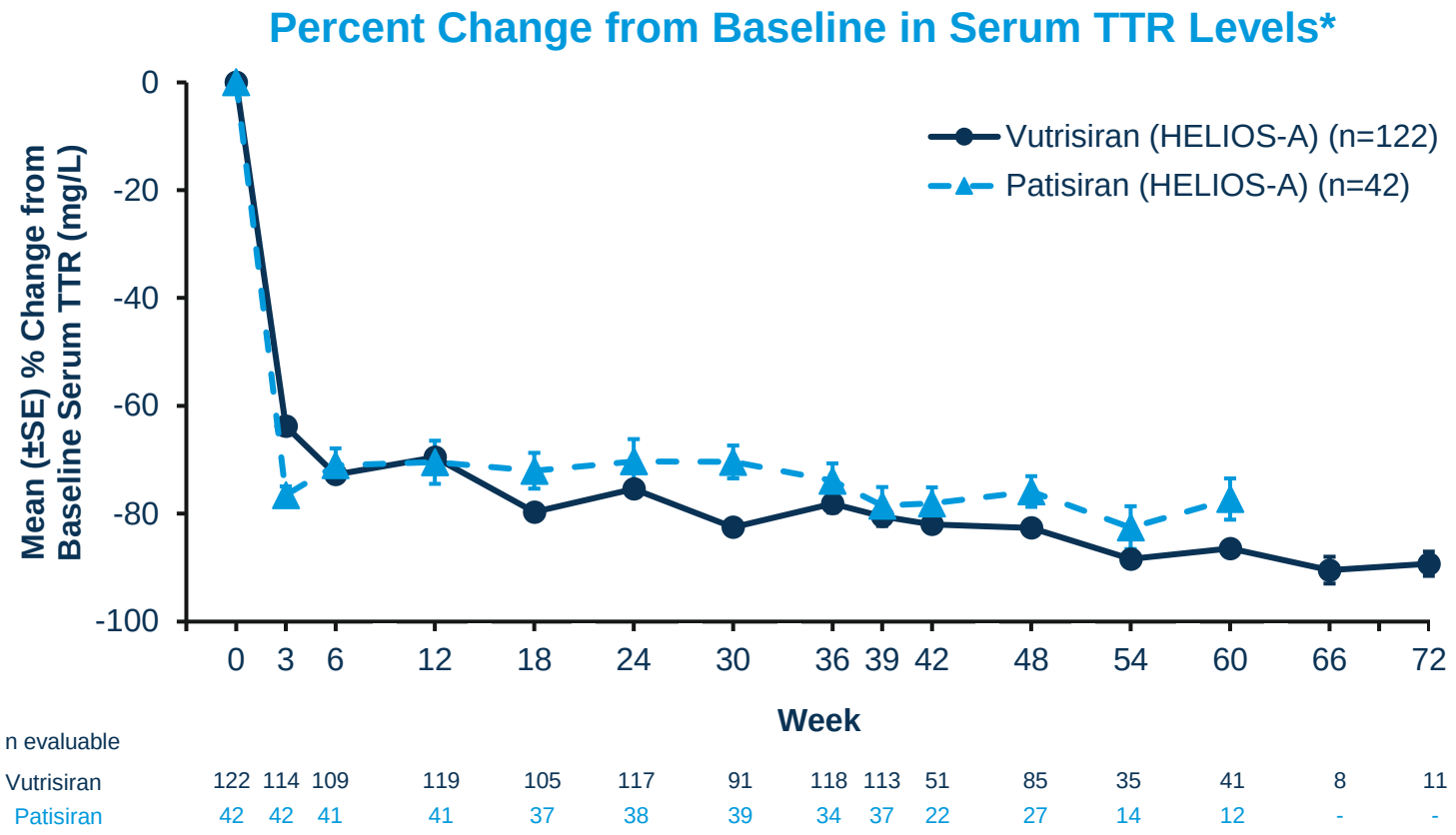


*NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. **At baseline, NT-proBNP geometric mean (SE) was 273.0 (42.2) ng/mL in the vutrisiran group (n=122) and 531.3 (86.7) ng/L in APOLLO placebo (n=75) group.** †Cardiac subpopulation was defined as patients who had pre-existing evidence of cardiac amyloid involvement (baseline left ventricular wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history). **At baseline, NT-proBNP geometric mean (SE) was 772.8 (195.0) ng/L in the vutrisiran cardiac subpopulation group (N=35) and 771.1 (151.1) ng/L in APOLLO placebo cardiac subpopulation (N=34) group.** ‡Number of evaluable patients.
CI, confidence interval; mITT, modified intent-to-treat; NT-proBNP, N-terminal pro–brain natriuretic peptide; SE, standard error.

Adams et al., PNS, June 2021

Rapid and Sustained Reduction in Serum TTR Levels with Vutrisiran Similar to Patisiran in HELIOS-A

- Vutrisiran achieved a mean steady-state* serum TTR reduction from baseline of 83% (SD: 14%), with maximum observed reduction of 98%



*Steady state was measured using Day 211 samples for vutrisiran.

SD, standard deviation; SE, standard error; TTR, transthyretin.

Adams et al., AAN, April 2021, updated to provide maximum reduction data

HELIOS-A Safety Summary*

Acceptable Safety Profile of Vutrisiran

The majority of AEs were mild or moderate in severity

- No drug-related discontinuations or deaths
- Two study discontinuations (1.6%) due to AEs in the vutrisiran arm by Month 9, both due to deaths, neither of which were considered related to study drug
  - One death due to COVID-19 pneumonia and the other due to iliac artery occlusion
- Two SAEs deemed related to vutrisiran by investigators:
  - Dyslipidemia and urinary tract infection
- AEs ≥10% in vutrisiran group included diarrhea, pain in extremity, fall, and urinary tract infection
  - Each of these events occurred at a similar or lower rate compared with the external placebo group
- Injection site reactions were reported in five patients (4.1%) receiving vutrisiran
  - All were mild and transient
- No safety signals regarding liver function tests, hematology, or renal function related to vutrisiran

HELIOS-A Safety Summary*,†

At least one event, n (%)	APOLLO†	HELIOS-A	
	Placebo (n=77) PY=96.1	Vutrisiran (n=122) PY=131.3	Patisiran (n=42) PY=43.2
AEs	75 (97.4)	114 (93.4)	40 (95.2)
SAEs	31 (40.3)	21 (17.2)	17 (40.5)
Severe AEs	28 (36.4)	15 (12.3)	12 (28.6)
AEs leading to treatment discontinuation	11 (14.3)	2 (1.6)	3 (7.1)
AEs leading to stopping study participation	9 (11.7)	2 (1.6)	2 (4.8)
Deaths	6 (7.8)	2 (1.6)	3 (7.1)

*Cumulative safety data from first dose of study drug to data cut-off date (November 10, 2020). †External reference to reflect the type of disease-related events commonly reported in this population.
AE, adverse event; PY, patient-years; SAE, serious AE.

Adams et al., AAN, April 2021

HELIOS-A 18-Month Data to Further Assess Vutrisiran

18-Month Results Expected Late 2021

Additional Secondary Endpoints

- Extend mNIS+7, Norfolk QOL, and 10-MWT dataset beyond 9 months with longer follow-up
- Assess new secondary endpoints: mBMI, R-ODS, serum TTR reduction

Exploratory Endpoints

- Further insights into potential benefit of vutrisiran on cardiac manifestations of disease

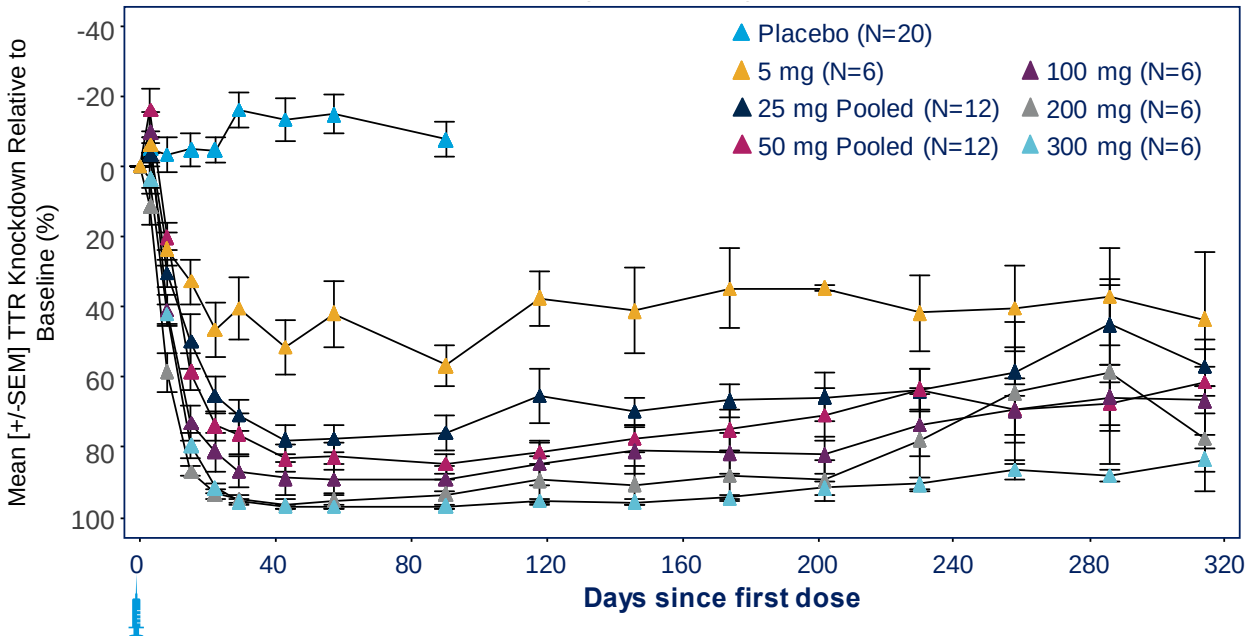
Exploratory endpoint	Measures
NT-proBNP	Cardiac stress
Left ventricular wall thickness	Cardiac amyloid burden
Longitudinal strain	Cardiac function
Technetium scintigraphy	Cardiac amyloid burden

Opportunity for q6M Vutrisiran Dosing Regimen

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

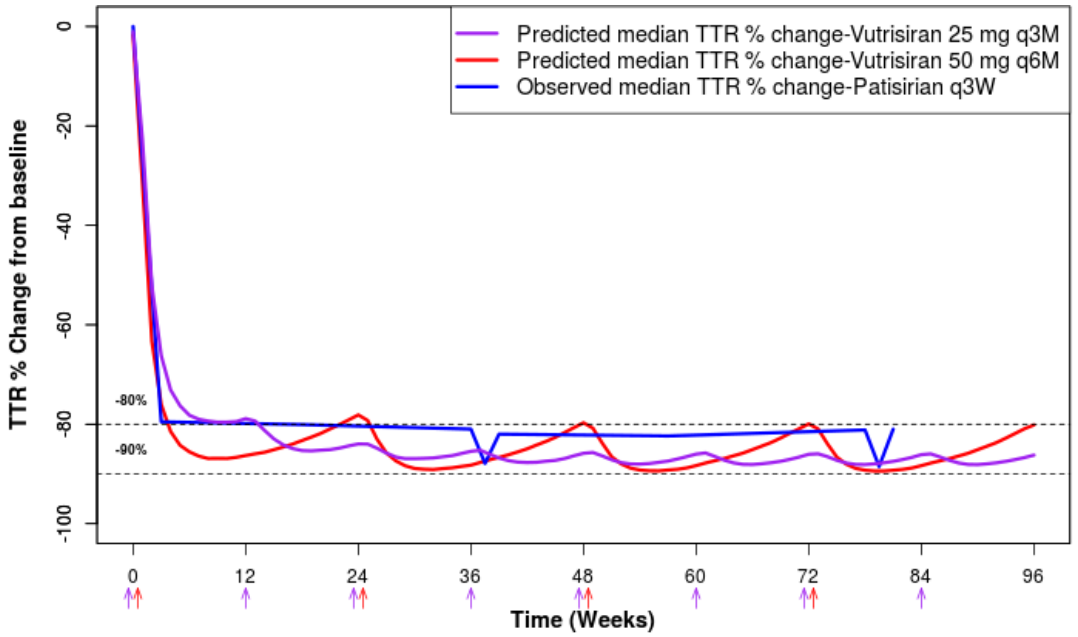
Phase 1 Study – Healthy Volunteers

- 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
- 50mg q6M vutrisiran dosing predicted to have similar TTR reduction as 0.3mg/kg q3W patisiran
- Comparable median TTR reduction at steady state predicted for both 25mg and 50mg repeat dosing

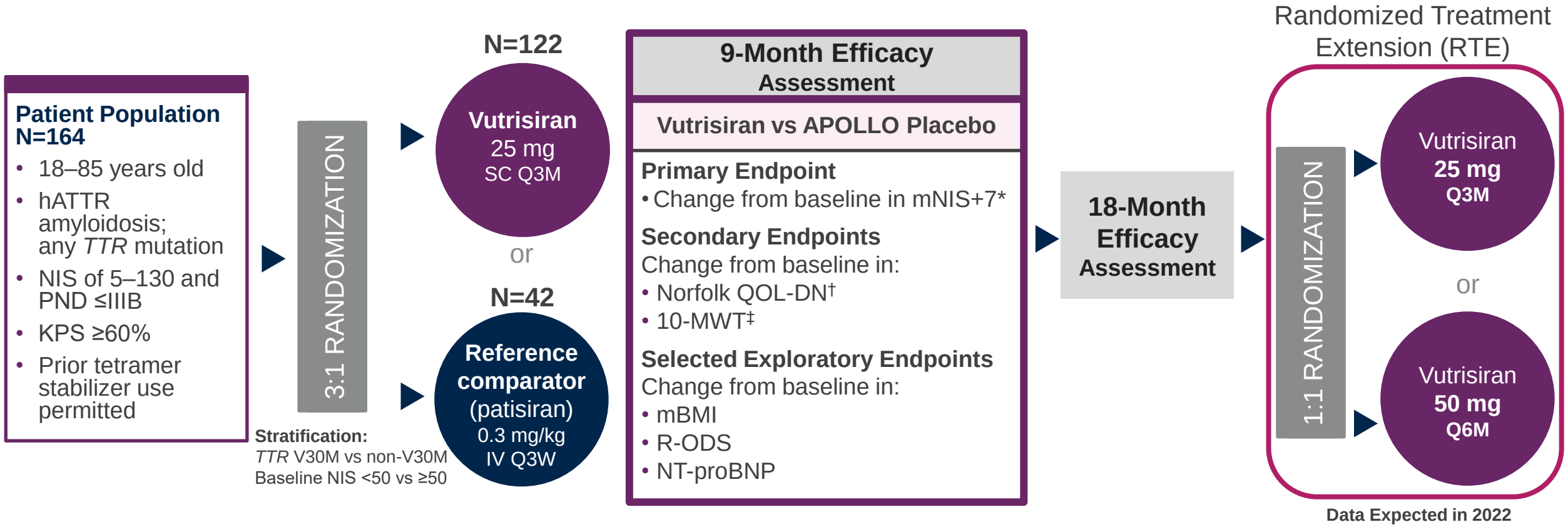


† Taubel J, et al. Phase 1 Study of ALN-TTRsc02, a Subcutaneously Administered Investigational RNAi Therapeutic for the Treatment of Transthyretin-Mediated Amyloidosis. ISA 2018: XVIIth International Symposium of Amyloidosis; Kumamoto, Japan; March 2018 (poster)

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

Vutrisiran HELIOS·A Phase 3 Study

Randomized, Open-Label Study in Hereditary ATTR Amyloidosis Patients with Polyneuropathy



*Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304). †Higher scores of Norfolk QOL-DN indicate worse quality of life (range, -4 to 136). ‡10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete two assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function.

10-MWT, 10-meter walk test;; IV, intravenous; KPS, Karnofsky performance status; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro–brain natriuretic peptide; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built overall disability scale; SC, subcutaneous; TTR, transthyretin.

Vutrisiran Key Milestones and Planned Next Steps

Regulatory Submissions
EU, BR, JP
Late 2021

HELIOS-A Topline 18-Month Results
Late 2021

If Approved, U.S. Launch
Early 2022

50mg q6M Data Readout
Late 2022

Agenda

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

Introduction and Overview of ATTR Amyloidosis
- Rena Denoncourt – Vice President, ATTR Amyloidosis Franchise Lead
- Patient Story – Dawn, caregiver and hATTR amyloidosis patient

Recent Vutrisiran Clinical Data in Patients with hATTR Amyloidosis with Polyneuropathy
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- Rena Denoncourt – Vice President, ATTR Amyloidosis Franchise Lead

Q&A Session

Patisiran Post-OLT Study Design

Phase 3b, Open-Label Study Conducted across Several European Countries[a]

Patient population (n=23)

- Age ≥18 years
- Received OLT for hATTR amyloidosis ≥12 months prior to study start
- Worsening PND score after OLT[b]
- KPS ≥70%
- NYHA class ≤II
- No previous or current use of patisiran or inotersen, and will not be using a TTR stabilizer during the study
- No liver allograft rejection episodes[c] ≤6 months prior to the study

Patisiran
0.3 mg/kg IV q3w
for 12 months

Primary endpoint:

- Average of Month 6 and Month 12 TTR percent reduction

Secondary endpoints:

- Change from baseline at Month 12 in:
  - NIS
  - Norfolk QOL-DN
  - COMPASS-31
  - R-ODS
  - mBMI

Safety (frequency and severity of AEs)

ClinicalTrials.gov Identifier: NCT03862807

Objective: To describe the 12-month efficacy and safety results of patisiran in patients with hATTR amyloidosis who have had polyneuropathy progression post-OLT

[a]Countries: UK, Sweden, France, Germany, Italy, Portugal, Spain. [b]Disease progression was defined as a documented increase in PND score, e.g., from I to II, II to IIIA, etc., compared with the pre-OLT assessment, or a documented increase in PND score between any two assessments post-OLT. [c]Including abnormal LFTs suggestive of possible allograft rejection

AE, adverse event;; COMPASS-31, Composite Autonomic Symptom Score 31-item questionnaire; IV, intravenous; KPS, Karnofsky Performance Status; LFT, liver function test; mBMI, modified body mass index; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; NYHA, New York Heart Association; OLT, orthotopic liver transplantation; PND, polyneuropathy disability; q3w, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin

Muñoz-Beamud F et al. PNS 2021: Poster 1

Baseline Demographics and Characteristics

Baseline demographics and characteristics	Safety analysis set (n=23)
Age, years, mean (SD)	58.1 (9.9)
Male, n (%)	13 (56.5)
Race, n (%)	
White	22 (95.7)
Asian	1 (4.3)
Age at hATTR amyloidosis diagnosis, years, mean (SD)	46.7 (11.7)
V30M genotype[a], n (%)	15 (65.2)
Previous TTR stabilizer use[b], n (%)	13 (56.5)
Age at liver transplant, years, mean (SD)	50.1 (10.8)
Time from hATTR amyloidosis diagnosis to OLT, years, mean (SD)	3.7 (3.0)
Time from OLT to first patisiran dose, years, mean (SD)	9.4 (5.1)
Immunosuppression regimens at baseline, n (%)	
Tacrolimus	10 (43.5)
Tacrolimus + mycophenolate	7 (30.4)
Other[c]	6 (26.1)
BMI, kg/m^2, mean (SD)	23.5 (3.6)
Serum TTR level, mg/L, mean (range)	202.1 (123.7–315.1)
NIS total score, mean (range)	60.3 (7.0–136.5)
Norfolk QOL-DN score, mean (range)	66.7 (16.0–98.0)
PND score, n (%)	
I: preserved walking, sensory disturbances	1 (4.3)
II: impaired walking but can walk without stick/crutch	9 (39.1)
IIIA: walk with 1 stick/crutch	7 (30.4)
IIIB: walk with 2 sticks/crutches	6 (26.1)
NYHA class, n (%)	
0: no heart failure	13 (56.5)
I	5 (21.7)
II	5 (21.7)

- Patients received an OLT an average of 3.7 years after diagnosis
- On average, patients received their first dose of patisiran 9.4 years after the OLT
- 13 (56.5%) patients had previously received a TTR stabilizer
- At baseline, the majority (56.5%) of patients had a PND score of IIIA/B
  - 16 patients (69.6%) had experienced a 1-unit increase from first documented PND score[d] to study baseline, prior to patisiran treatment
  - 4 patients (17.4%) experienced a 2-unit increase and 3 patients (13.0%) experienced a 3-unit increase
- 10 (43.5%) patients had NYHA class I/II

[a]Other genotypes include: S77T (3), G47A (1), G47V (1), L12V (1), F64L (1), and T116S (1). [b]Tafamidis in 11 (47.8%) patients; diflunisal in 2 (8.7%) patients. [c]Other immunosuppression regimens at baseline include: everolimus (1), ciclosporin (1), tacrolimus + everolimus (1), tacrolimus + azathioprine (1), ciclosporin + everolimus (1), ciclosporin + mycophenolate (1). [d]First documented PND score was either the most recent PND score prior to OLT, or first post-OLT PND score if no PND score prior to OLT

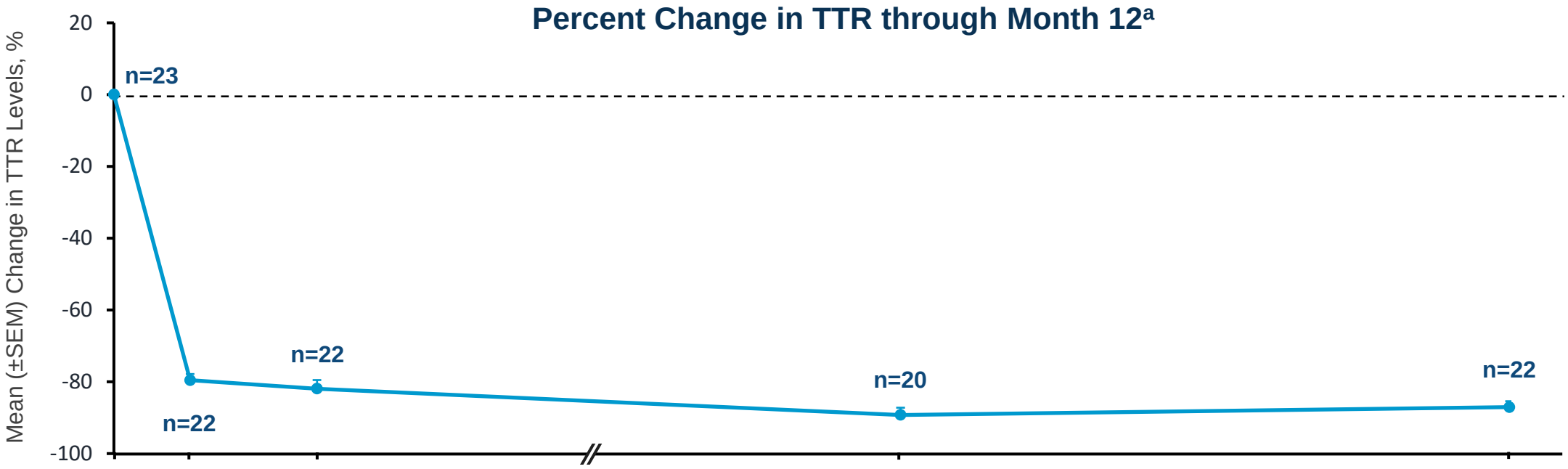
BMI, body mass index; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; NYHA, New York Heart Association; OLT, orthotopic liver transplantation; PND, polyneuropathy disability; SD, standard deviation; TTR, transthyretin; V30M, valine to methionine at position 30 variant

Muñoz-Beamud F et al. PNS 2021: Poster 1

Rapid and Sustained Reduction in Serum TTR Levels with Patisiran

Primary Endpoint

- Median (95% CI) TTR percent reduction from baseline (average of Month 6 and Month 12) was 91.0 (86.1, 92.3)



	BL	Wk 1–2	Wk 3	Month 6	Month 12
Mean (±SEM) TTR level, mg/L	202.1 (11.3)	41.1 (4.1)	35.5 (4.5)	21.2 (3.7)	24.9 (2.7)
Mean (±SEM) reduction from baseline, %	–	79.6 (1.7)	81.9 (2.4)	89.2 (2.0)	87.1 (1.7)

[a]Data for safety analysis set shown

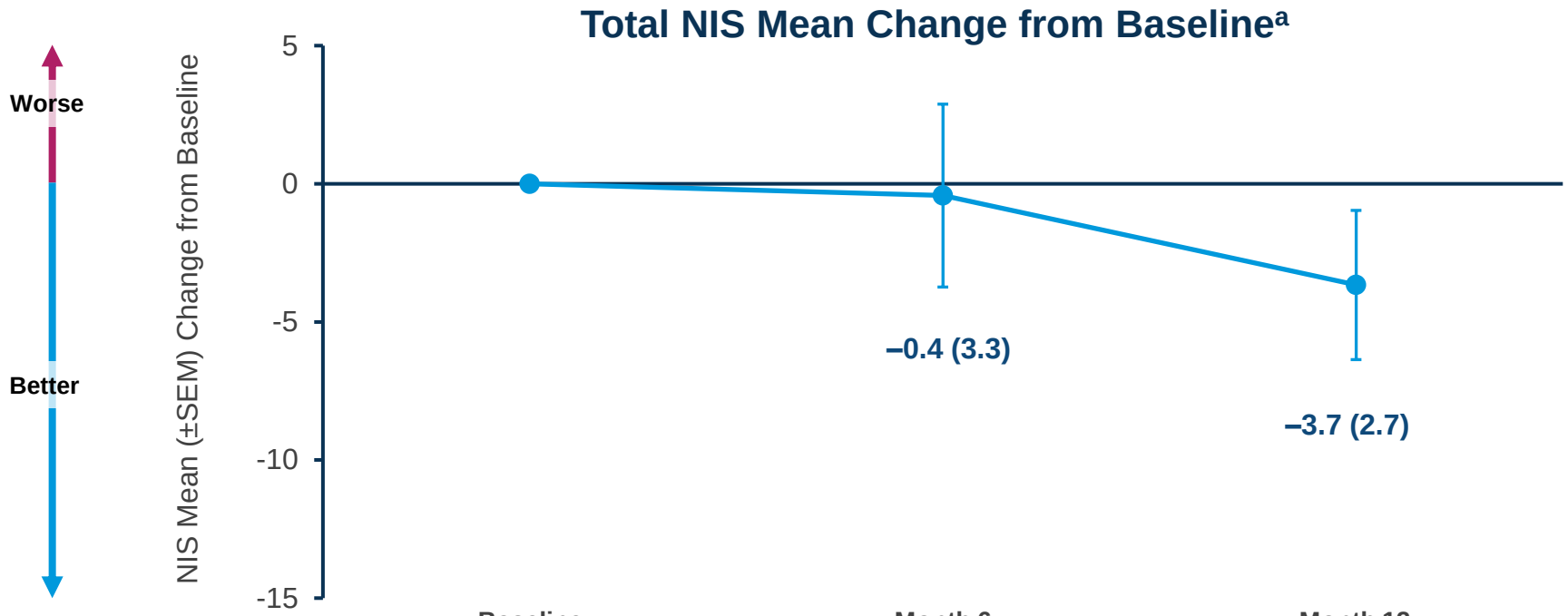
BL, baseline; CI, confidence interval; SEM, standard error of the mean; TTR, transthyretin; Wk, week

Muñoz-Beamud F et al. PNS 2021: Poster 1

Improvement in Polyneuropathy Disease Manifestations with Patisiran

Secondary Endpoints at Month 12

- Improvement in neuropathy, as demonstrated by a decrease in mean total NIS from baseline



	Baseline	Month 6	Month 12
n	21	20	20
Mean (±SEM)	60.0 (8.9)	58.6 (9.1)	55.3 (10.1)
Mean change from baseline (±SEM)	–	–0.4 (3.3)	–3.7 (2.7)

- Improvement or stability was also seen in all other secondary endpoints of quality of life, autonomic symptoms, disability and nutritional status

[a]Data for the per protocol analysis set shown. Twenty-one patients were included in the per protocol analysis set (meeting the criteria of ≤2 missing doses due to COVID-19)
NIS, Neuropathy Impairment Score; SEM, standard error of the mean. Muñoz-Beamud F et al. PNS 2021: Poster 1

Patisiran Post-OLT: Summary of Safety

Majority of AEs Were Mild or Moderate

- Common adverse events (AEs) were consistent with those seen in the Phase 3 APOLLO study[1]
  - The most common AE was diarrhea (34.8%)
  - 6 (26.1%) patients experienced infusion-related reactions (IRRs)
- 13 serious adverse events (SAEs) reported in 5 (21.7%) patients; 1 SAE (IRR) considered related to patisiran
- No discontinuations due to AEs and no deaths occurred on study
- All 23 patients completed the study; 1 patient discontinued treatment but completed the study
- Liver transplant rejection in 1 patient deemed unrelated to patisiran by investigator; biopsy was consistent with mild acute cellular rejection likely due to inadequate immunosuppression (IS)
  - Patient remained on study drug and completed study
  - IS regimen modified; LFTs remained stable, mostly ranging 1–2×ULN
- Other safety:
  - LFTs were normal in the majority of patients
  - Transient ALT elevation >3×ULN associated with cholangitis in 1 patient deemed unrelated to patisiran by investigator
  - No cases of platelet count <50,000/mm^3

Patients with ≥1 event, n (%)	Safety analysis set (n=23)
Any AE	23 (100)
AEs reported in ≥10% of patients	
Diarrhea	8 (34.8)
IRR	6 (26.1)
Peripheral edema	5 (21.7)
Back pain	5 (21.7)
Cardiac failure	3 (13.0)
Fall	3 (13.0)
Fatigue	3 (13.0)
Headache	3 (13.0)
Pyrexia	3 (13.0)
UTI	3 (13.0)
AE related to study drug	8 (34.8)
Any SAE[a]	5 (21.7)
SAE related to study drug[b]	1 (4.3)
AE leading to discontinuations	0
AE leading to study drug interruption	5 (21.7)
AE leading to death	0

[a]Only term reported in >1 patient was cardiac failure, occurring in 3 patients with history of cardiomyopathy. [b]Occurred after patient's first infusion, with symptoms of dizziness and gait instability requiring overnight hospitalization. The event resolved the following day without intervention and without a change in patisiran treatment

AE, adverse event; ALT, alanine transaminase; IRR, infusion-related reaction; IS, immunosuppression; LFT, liver function test; OLT, orthotopic liver transplantation; SAE, serious adverse event; ULN, upper limit of normal; UTI, urinary tract infection; Muñoz-Beamud F et al. PNS 2021: Poster 1

1. Adams et al. *N Engl J Med* 2018;379:11–21.

Patisiran Phase IV Observational Study

A Multicenter Observational Study to Evaluate the Effectiveness of Patisiran in Patients With Polyneuropathy of hATTR Amyloidosis with a V122I or T60A Variant

N = 68
Patient Population:

- hATTR amyloidosis with polyneuropathy and a documented V122I or T60A variant
- Exposure to commercial patisiran in one of 3 cohorts
  - Prospective cohort: Naïve to patisiran at time of enrollment with intention to initiate patisiran
  - Mixed cohort: On commercial patisiran for less than 12 months at enrollment
  - Retrospective cohort: Have been on commercial patisiran for 12+ months prior to enrollment, regardless of current treatment status

Observational for 12 Months

Primary endpoint

- Proportion of patients with stable or improved PND score at 12 months relative to baseline

Select Exploratory Endpoints

- Change from baseline to 12 months for the following parameters:
  - Norfolk QOL-DN score
  - COMPASS-31 score
  - BMI
  - NT-proBNP
  - KCCQ score

ClinicalTrials.gov Identifier: NCT04201418

Study Goal

- To evaluate the effectiveness of patisiran on ambulatory status in patients with hATTR amyloidosis with polyneuropathy who have a V122I or T60A variant

Enrollment completed June 2021

Results expected 2022

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Alnylam's ATTR Amyloidosis Franchise Opportunity
- Rena Denoncourt – Vice President, ATTR Amyloidosis Franchise Lead

Q&A Session

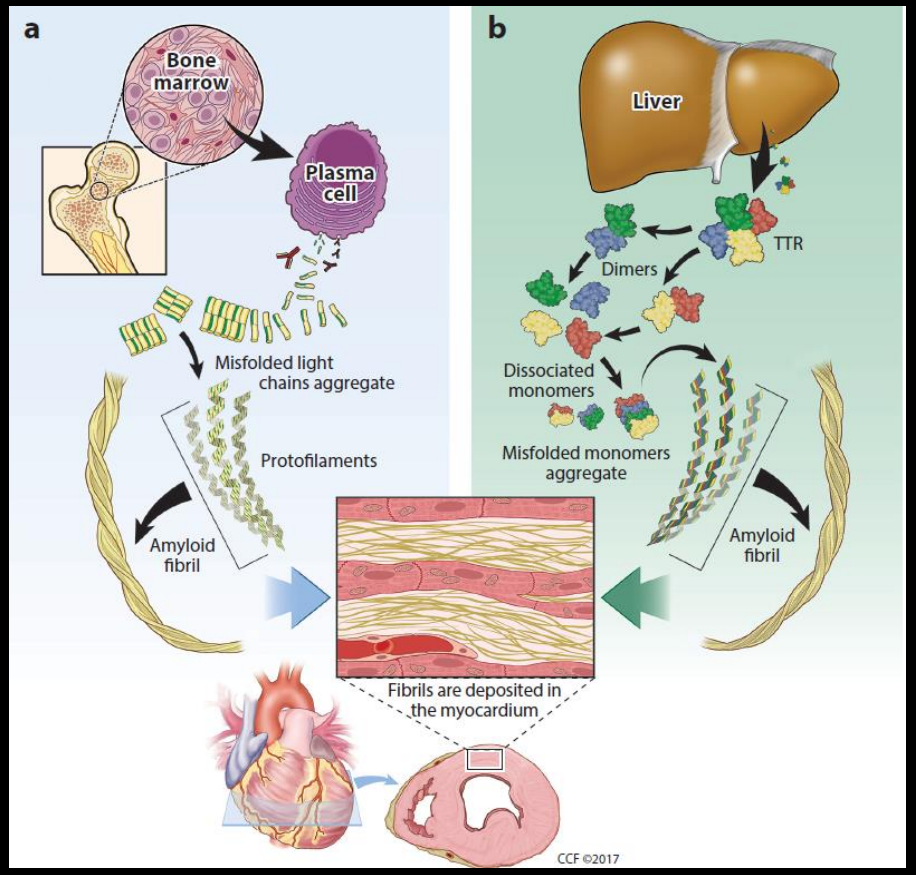
Alnylam RNAi Roundtable: ATTR amyloidosis

Mat Maurer, MD
Columbia University Medical Center
Arnold and Arlene Goldstein Professor of Cardiology
July 16th, 2021

Disclosures

- I have consulted for and/or received support from several sources for my research:
  - NIH/NIA/NHLBI
  - GSK
  - Akcea, Inc
  - Alnylam Pharmaceuticals, Inc
  - Abbott, Inc
  - -Eidos
  - -Prothena
  - -Ionis Pharmaceuticals
  - -Pfizer, Inc.
  - -Intellia

Two Main Types of Cardiac Amyloidosis



- Differences in
  - Precursor Protein / Biology
  - Natural History / Prognosis
  - Genetics
  - Treatment

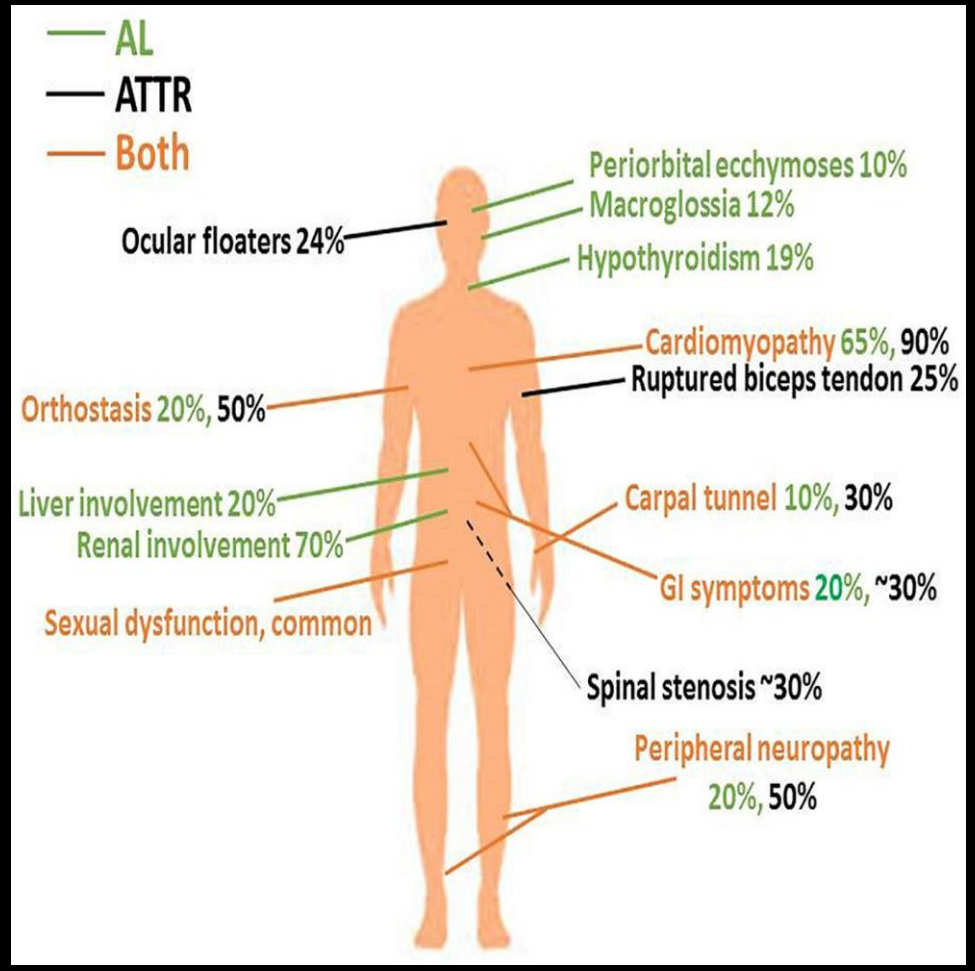
Cleveland Clin. J. Med. 84(12 Suppl. 3):12–26
Circulation. 2017;135(14):1357-1377

Different Types of Cardiac Amyloidosis

Features	AL	ATTRh	ATTRwt
Epidemiology Average at diagnosis Gender	5th to 9th decade Equal male and female	3rd to 8th decade Male predominance	7th to 10th decade 80-90% Males
Biology Precursor protein Genetic cause	Light chain None	Mutant TTR Autosomal dominant	TTR None
Organ involvement (%) Cardiac Extra-cardiac	~60-70% Nephrotic syndrome Peripheral/Autonomic Neuropathy	Most Peripheral/Autonomic Neuropathy	All CTS, LSS, Tendinopathy
Prognosis	Depends on Stage 4-6 months with advanced HF	Depends on Stage 3-12 years	Depends on Stage 2-6 years
Therapy	Anti-plasma cell therapy	Silencers and Stabilizers	Stabilizers

Annu Rev Med. 2020 Jan 27;71:203-219

Multi-systemic Disease with Significant Risk of Misdiagnosis and Delayed Diagnosis



Varga C et al. Blood Rev. 2021;45:100720

- 75% saw > 3 physicians before diagnosis made
- 63% > 6 months to diagnosis
- 44% received an incorrect diagnosis first
- 31% required air travel to establish diagnosis
- Only 18% of these patients with cardiac AL had the correct diagnosis made by a cardiologist
- Cardiologists are the most common subspecialists to make a misdiagnosis – most commonly - hypertrophic cardiomyopathy

Lousada et al, European Hematology Association (EHA) 22nd Annual Congress 2017; June 22–25, 2017

Diagnostic Tests and Their Role in the Various Phases of Evaluation and Management of Cardiac Amyloidosis

Phase of Workup	Imaging and Biomarkers of Cardiac Amyloidosis			
	ECHO	MRI*	"Bone Tracers" Scintigraphy	BNP
Suspicion	+++	++	+/– (TTR)	++
Early diagnosis	+/–	++	++ (TTR)	+/–
Definite diagnosis	+/–	+/–	+++	+/–
Etiologic diagnosis	+/–	+/–	+++ (TTR)	–
Functional evaluation	+++	++	+ (MIBG)	+/–
Prognostic stratification	++	+	+	+++
Amyloid burden	–	++	+/–	–
Response to therapy	+/	+/–	+/–	+++ (AL)

Circulation. 2017;135:1357–1377.

Advantages, Limitations and Novel Insights of Imaging Modalities

Modality	Advantages	Limitations	Novel insights
Echocardiography	• Widely available and relatively inexpensive • Can provide insight into morphological and functional cardiac changes • Emerging role for strain imaging for diagnosis and prognosis	• Best for assessing advanced LV remodelling (although diastolic dysfunction might suggest early changes) • Limited by patient-specific factors (eg, windows, image artifacts) • Morphologic and functional changes nonspecific (amyloid abnormalities might overlap with other cardiomyopathies, cannot differentiate ATTR from AL) • Strain imaging not widely clinically available	• LV wall thickness of ATTR > AL, usually • Apical sparing very suggestive of cardiac amyloid • Strain imaging might be prognostic • Myocardial contraction fraction might be useful for identification and is prognostic for ATTR
Nuclear (^{99m}Tc-PYP, ^{99m}Tc-DPD)	• Highly sensitive for TTR amyloid due to either mutation or wild-type • Can differentiate ATTR from AL • ^{99m}Tc-PYP available for use in United States and Canada	• Negative result does not exclude AL cardiac amyloid • Minimal radiation exposure (equivalent to mammogram) • ^{99m}Tc-DPD not FDA-approved	• Prevalence of TTR cardiac amyloid is higher than previously recognized in conditions such as HFPEF and aortic stenosis • Extent of myocardial retention correlates with poorer prognosis • TTR amyloid deposits accumulate slowly • Clinical disease progression occurs despite lack of changes with imaging
CMR	• High spatial and temporal resolution • No radiation exposure, reproducible (excellent for serial assessment of function, morphology) • Cine-CMR and native T1 mapping do not require contrast • Tissue characterization might enable disease detection before advanced changes in LV morphology	• Contraindicated in patients with ferromagnetic implants (eg, pacemaker; frequently among CA patients with conduction disease) • Gadolinium contraindicated in patients with advanced renal insufficiency • Patients with claustrophobia or advanced HF might not tolerate CMR • LGE patterns nonspecific; might require biopsy to establish diagnosis and distinguish amyloid subtypes (TTR, AL)	• LGE- and ECV-based tissue characterization provide incremental diagnostic utility beyond standard morphological indices (eg, LVH, EF) • LGE pattern and ECV elevation magnitude might help to distinguish between amyloid subtypes (TTR and AL) • LGE and ECV stratifies prognosis (mortality) among amyloid patients independent of LV morphology, functional, and biomarker indices

Canadian Journal of Cardiology 32(9) 2016, 1166.e1-1166.e10

Discordance Between Voltage /Wall Thickness

Males

	LQV	Symm. LVH	tQRS / (LVWT /$h^{2.7}$)
Sens	44%	91%	78%
Spec	93%	27%	81%
LR+	6.6	1.3	3.6
LR-	0.6	0.3	0.2

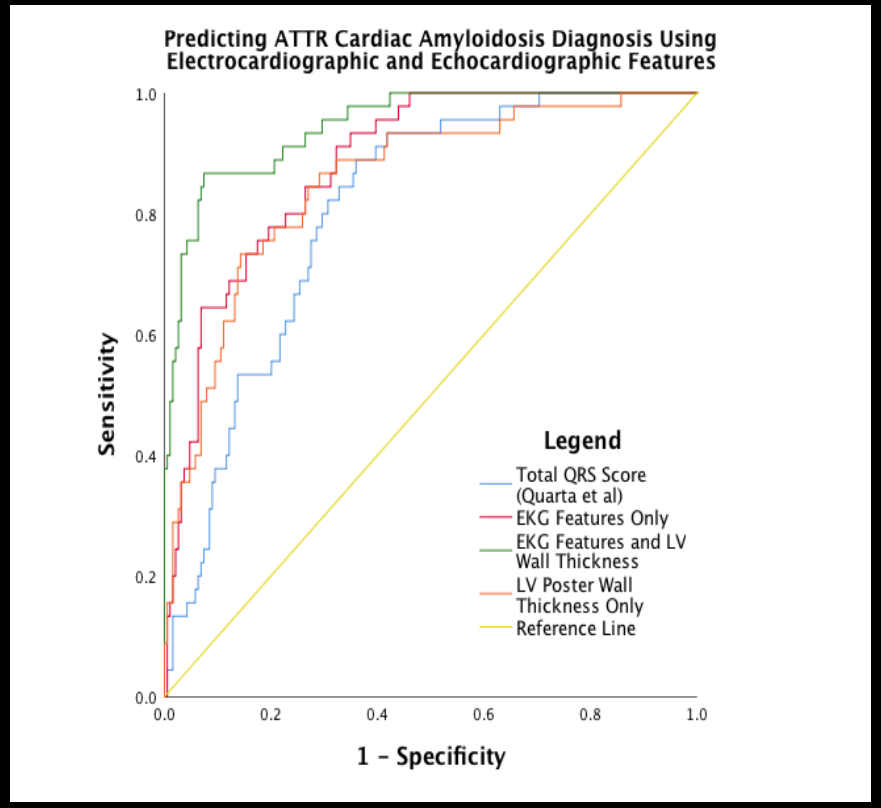
Females

	LQV	Symm. LVH	tQRS / LVWT
Sens	52%	91%	76%
Spec	91%	23%	81%
LR+	5.7	1.2	3.3
LR-	0.5	0.4	0.3

Total QRS/LVWT: Males, cutoff 8.4; Females, cutoff 7.7

Total QRS/LVWT/$h^{2.7}$: Males, cutoff 36.4; Female, cutoff 27.3

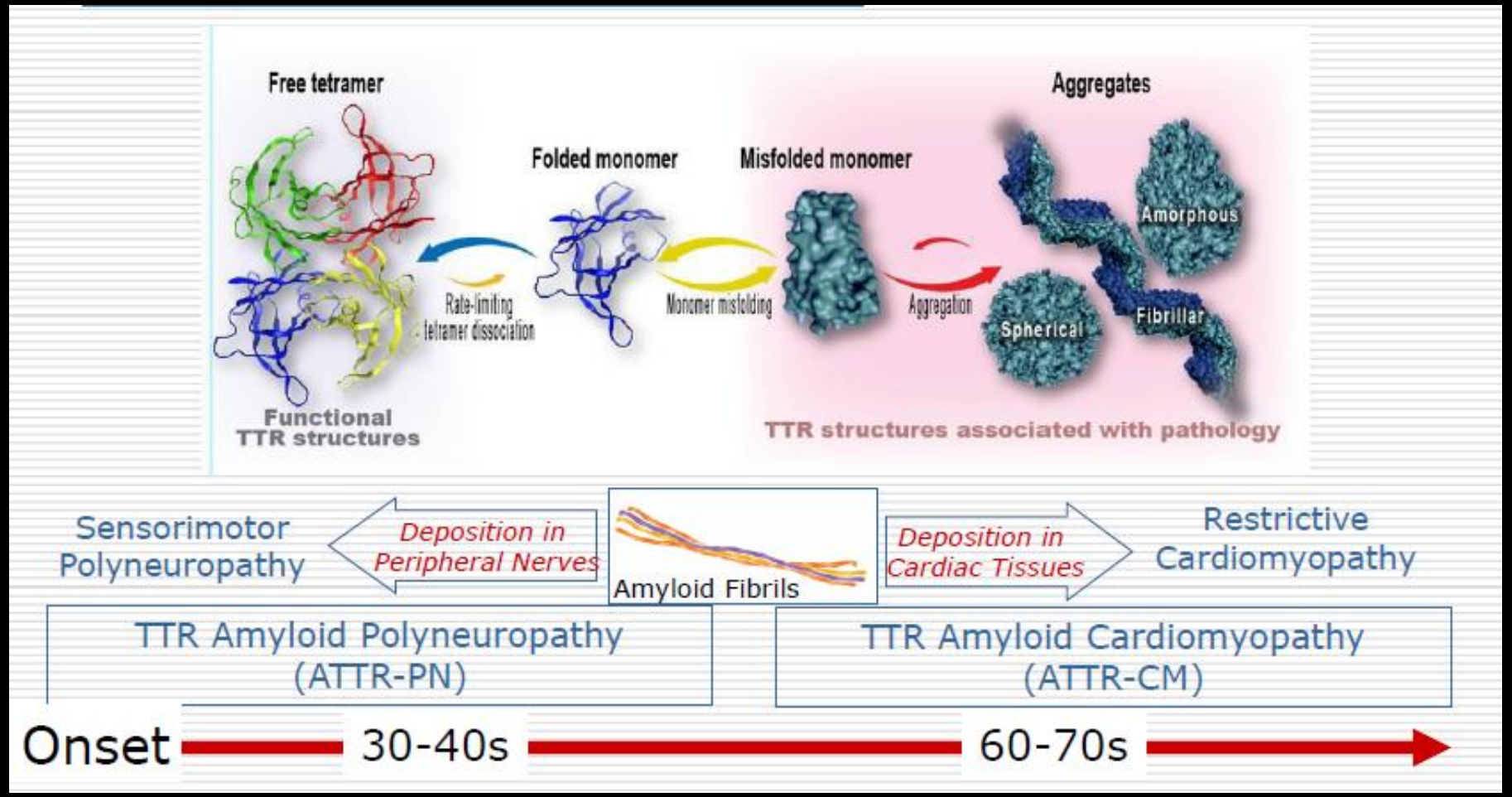
Leveraging AI and Machine Learning to Facilitate a Diagnosis of Cardiac Amyloidosis



Model	AUC (95% CI)	P value
Total QRS Score (Quarta et al)	0.80 (0.74-0.87)	<0.001
EKG Features Only	0.88 (0.84-0.93)	<0.001
EKG Features + LV Thickness	0.945 (0.91-0.98)	<0.001
LV Poster Wall Thickness Only	0.85 (0.79-0.91)	<0.001

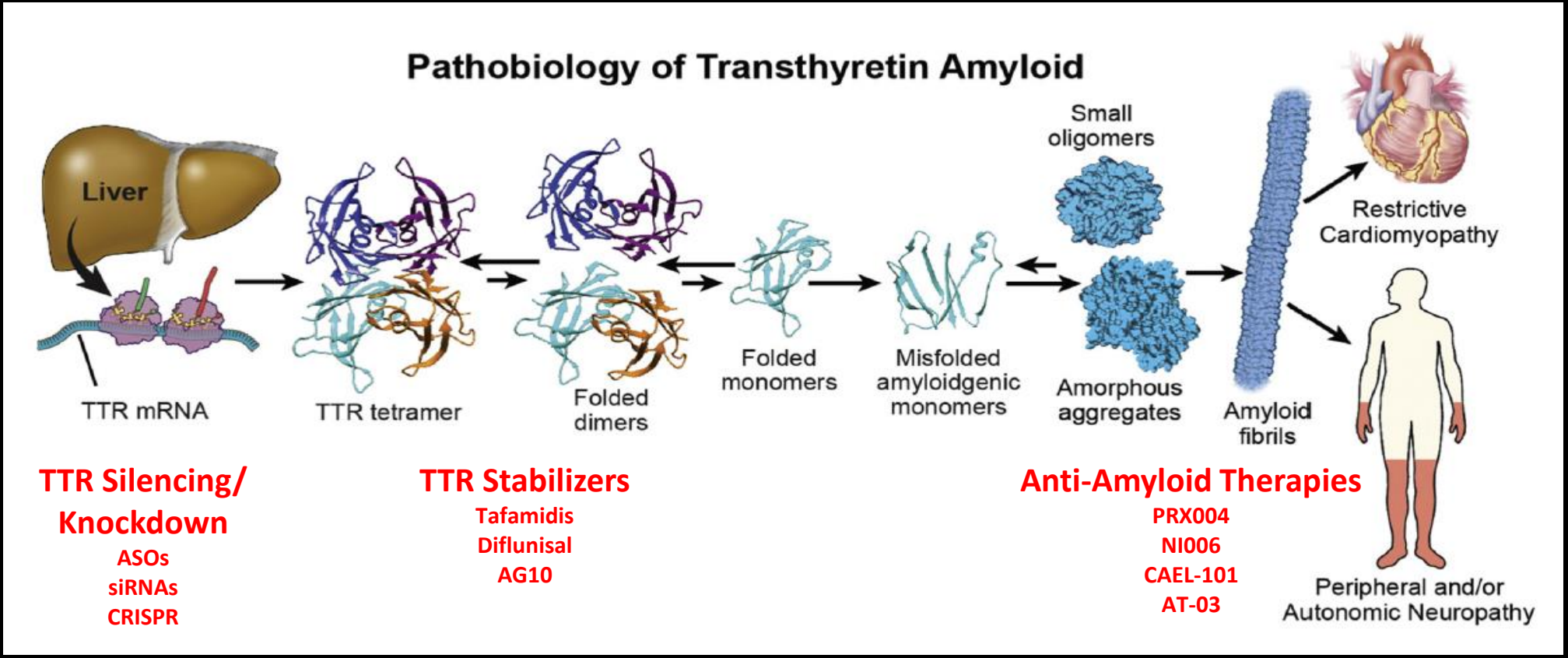
JACC 77 (18); Supplement 1: 529

Pathogenesis of ATTR Amyloidosis
Multiple Manifestations of One Disease



Slide courtesy of Jeff Kelly, PhD

Approved and Investigational Therapies for Transthyretin Amyloidosis have Emerged from Elucidation of Underlying Biology

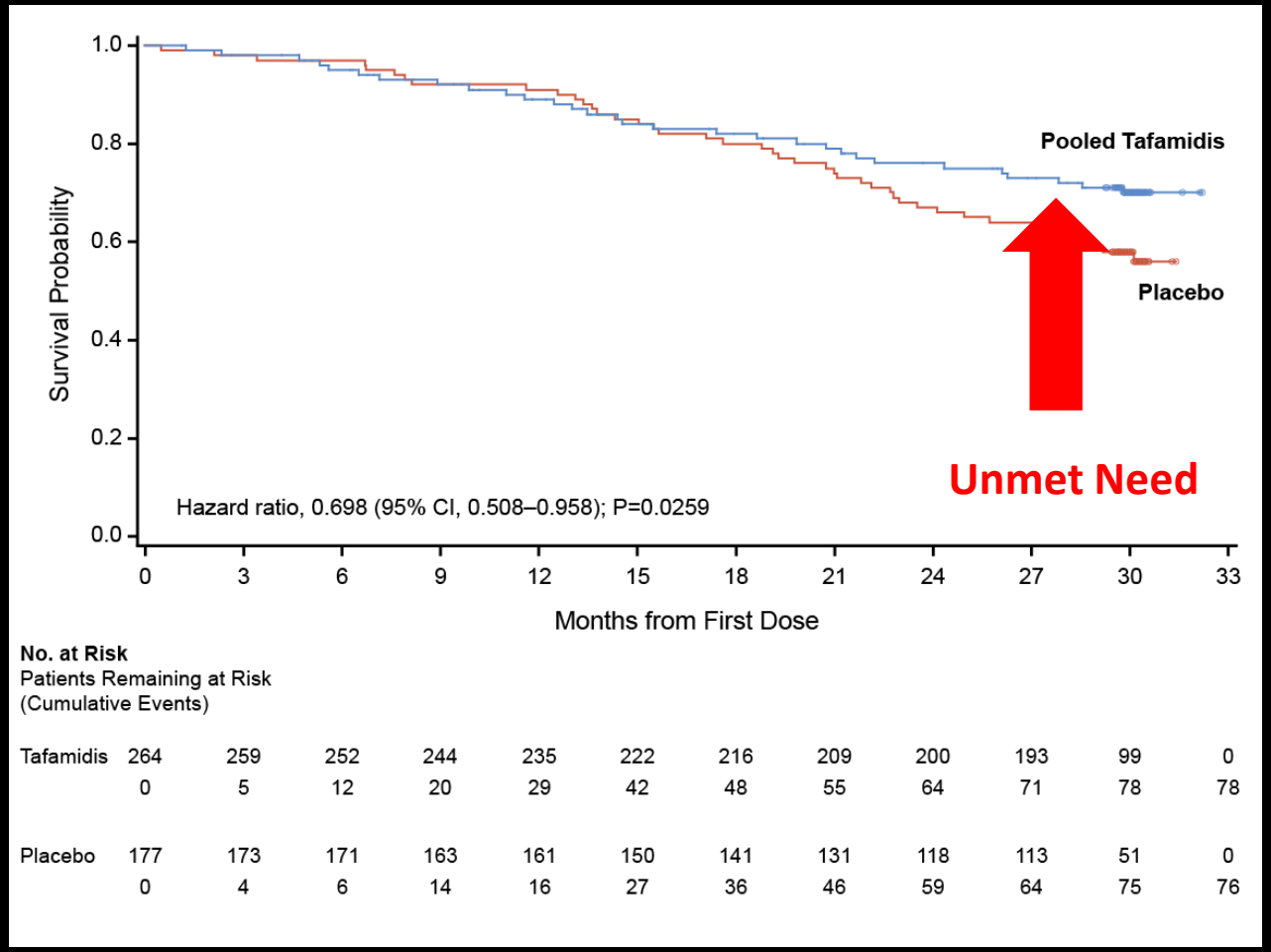


JACC. 2019;73(22):2872-2891. Currently silencer inotersen and silencer patisiran are approved in the U.S. for treating the PN of hATTR amyloidosis; clinical studies are ongoing evaluating their use for the treatment of wt & hATTR-CM. FDA has not found the investigational treatments discussed to be safe or effective for the indications under investigation; stabilizer tafamidis is approved in the U.S. for treating ATTR-CM only; diflunisal, an NSAID, is currently used off-label in the U.S. for treating ATTR amyloidosis; all other referenced therapies are investigational

While Tafamidis Reduces All-cause Mortality and CV Hospitalizations, Significant Unmet Patient Need Remains in ATTR

30% reduction (P=0.026) in overall mortality with tafamidis compared to placebo (need to treat 7-8 patients to prevent one death over 2 ½ years). However, 3 out of 10 tafamidis-treated patients died by Month 30.

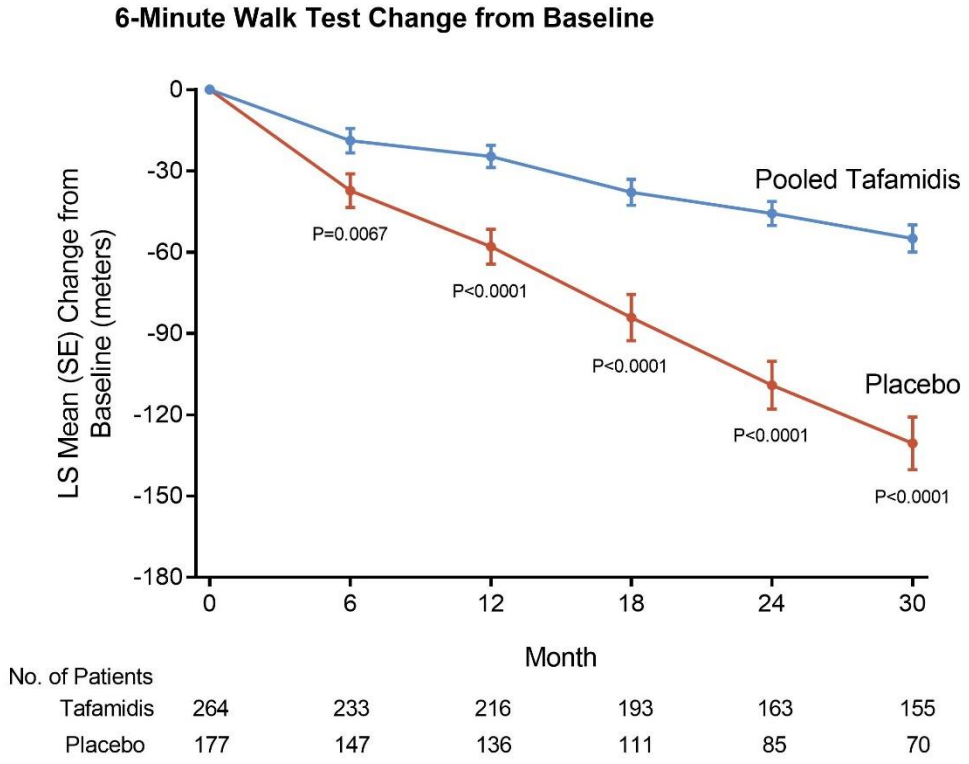
32% reduction in the rate of CV hospitalization with tafamidis compared with placebo (need to treat 4 patients to prevent 1 CV hospitalization per year). On average, each tafamidis-treated patient will have 1 CV hospitalization every two years.

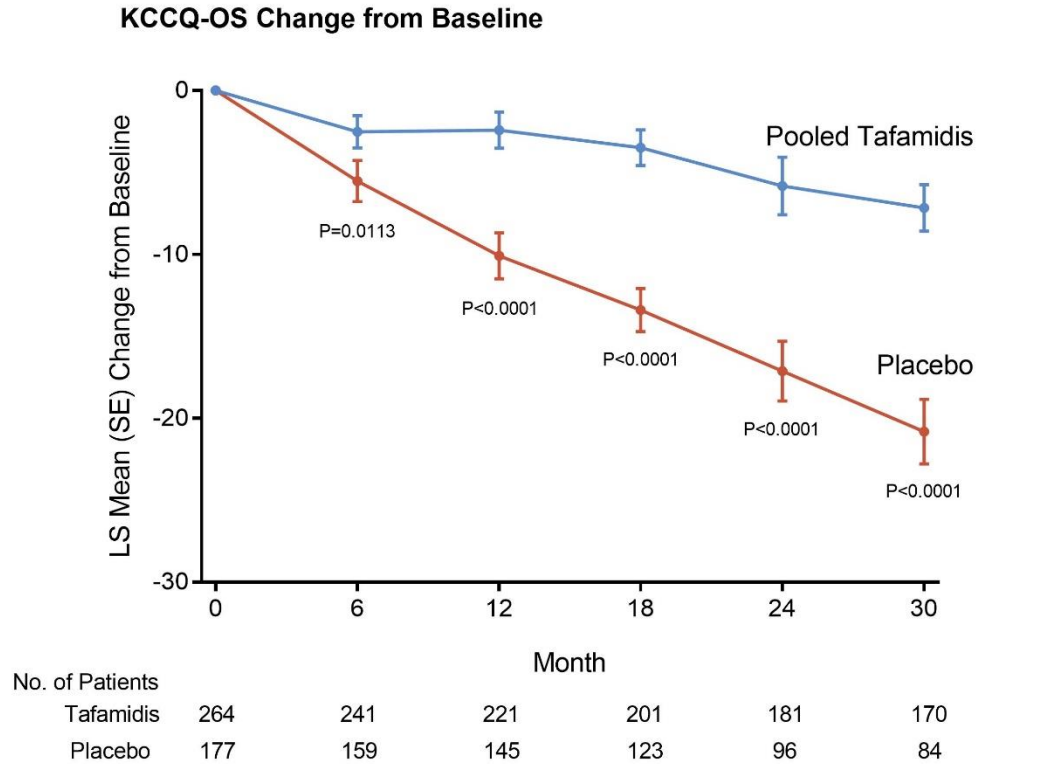


Maurer MS, et al. N Engl J Med. 2018 Aug 27.

While Tafamidis Reduced the Decline in Functional Capacity & QOL Relative to Placebo, the Average Patient didn't Feel or Function Better than at Baseline Based on 6MWT/KCCQ-OS -

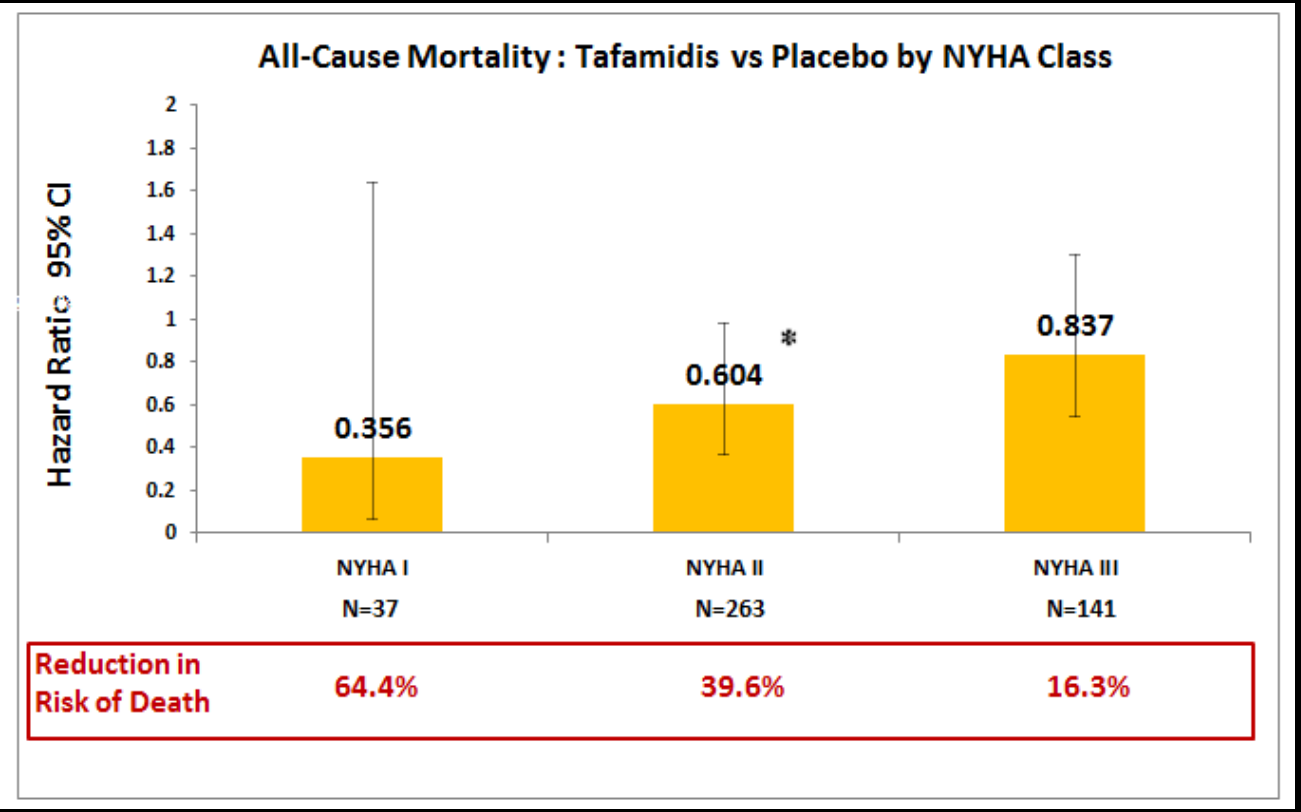
Pointing Again to Significant Unmet Need in ATTR Amyloidosis





Maurer MS, et al. N Engl J Med. 2018 Aug 27.

Earlier Treatment in ATTR-CM Affects Patient Outcomes



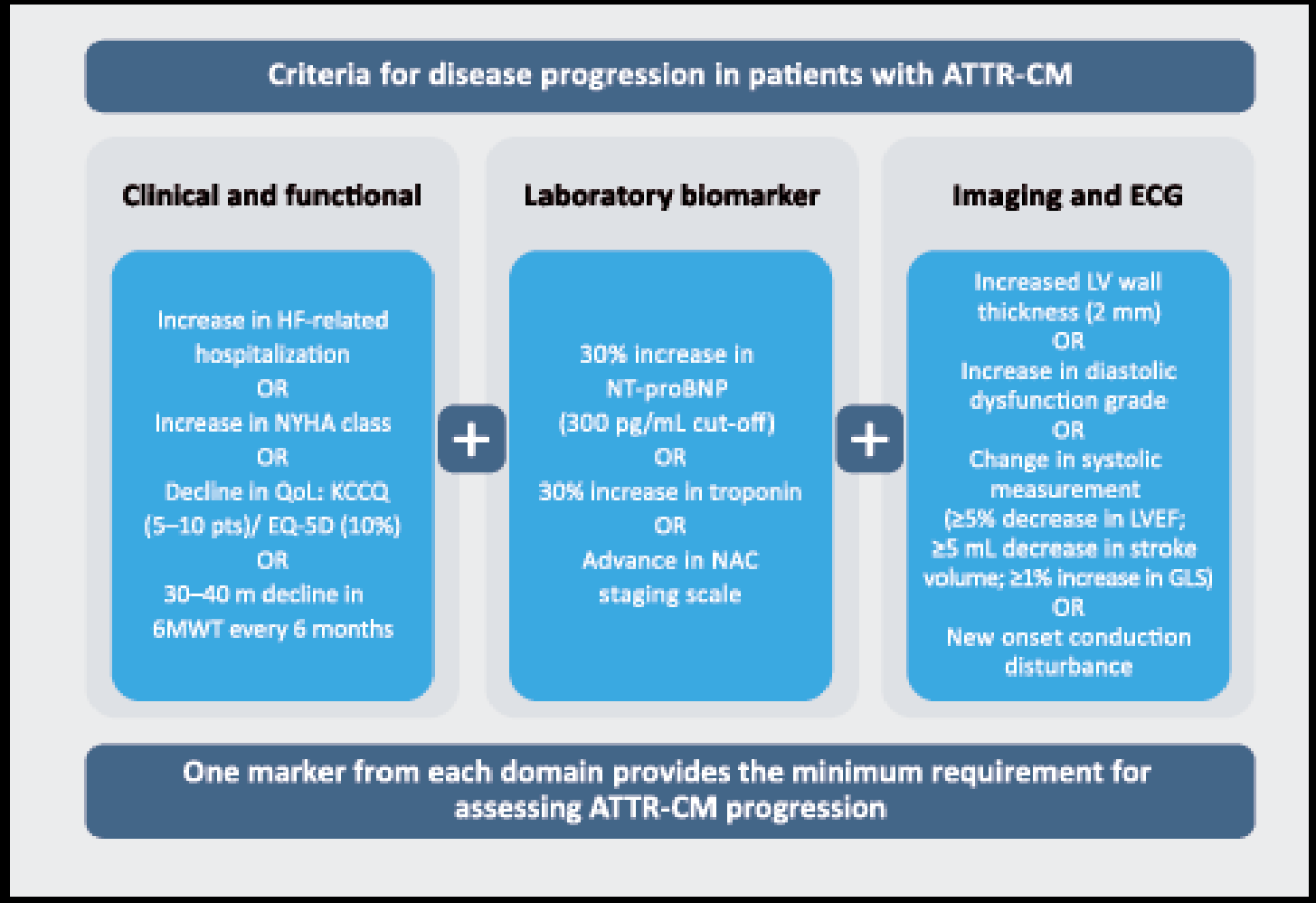
Maurer MS, et al. N Engl J Med. 2018 Aug 27.

Expert Consensus on Monitoring of Disease Progression

Tool and domain	Clinical feature	Threshold indicating disease progression	Recommended frequency of measurement
Clinical and functional			
Clinical and medical history	Cardiovascular-related hospitalizations	Worsening indicated by any hospitalization (related to HF decompensation) in a 6-month period	6 months
HF class: NYHA class	Stepwise class change (plus or minus) should indicate progression or amelioration/improvement, respectively	One class increase (note: must be measured during a 30-day period of stability)	6 months
QoL: EQ-5D tool and KCCQ	Description of measurements	Five-point decrease in KCCQ represents deterioration; 10-point decrease in KCCQ represents moderate deterioration; 10% decline in EQ-5D score represents deterioration	6–12 months
Functional capacity	6MWT	Decrease of 30–40 m every 6 months (in the absence of obvious non-cardiovascular cause)	6 months
Biomarkers and laboratory markers			
Biomarkers and laboratory markers	NT-proBNP	30% increase with 300 pg/mL cut-off To be measured during a 30-day period of clinical stability and under same atrial rhythm	6 months
	Troponin (high-sensitivity) assay	30% increase	6 months
	Clinical staging system	Advance in NAC staging score	6 months
Imaging parameters and ECG			
Echocardiography	LV measures wall thickness/mass	≥2-mm increase in LV wall thickness	6–12 months
	Systolic function measurements	≥5% decrease in LV ejection fraction decrease; ≥5 mL decrease in stroke volume and ≥1% increase in LV global longitudinal strain	12 months
	Diastolic dysfunction worsening, e.g. using diastolic functioning grade	Stepwise increase in diastolic functioning grade; consistent deterioration in diastolic function	12 months
ECG/Holter ECG	New-onset of arrhythmic/conduction disturbances	New-onset bundle branch block New-onset AV block (of any degree) Sinus pauses, sinus node dysfunction, AF with a very slow ventricular response without pharmacologic treatment (<50 bpm)	6 months

European Journal of Heart Failure (2021) doi:10.1002/ejhf.2198

Expert Consensus on Monitoring of Disease Progression



European Journal of Heart Failure (2021) doi:10.1002/ejhf.2198

Summary

- Emerging therapies for ATTR amyloidosis have been developed from translational research which has elucidated biologic mechanisms.
- A large portion of patients with ATTR amyloidosis remain undiagnosed and the diagnosis continues to be made in late stage patients.
- Patients and clinicians may someday be in the enviable position of choosing among different approved therapies across the spectrum of ATTR amyloidosis but research is needed to guide this process of shared decision making.

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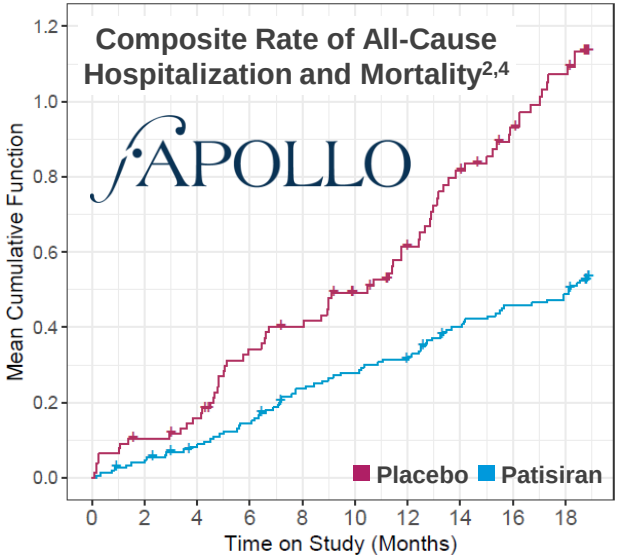
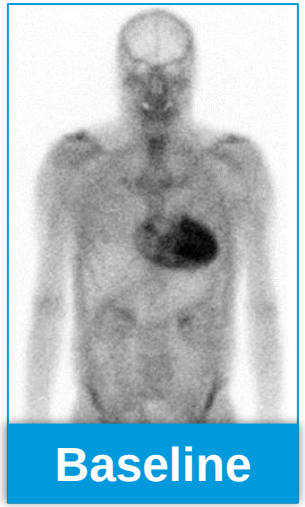
Evidence for Investigational RNAi Therapeutics in ATTR Cardiomyopathy[1]

Exploratory & Post-hoc Data from APOLLO[2]



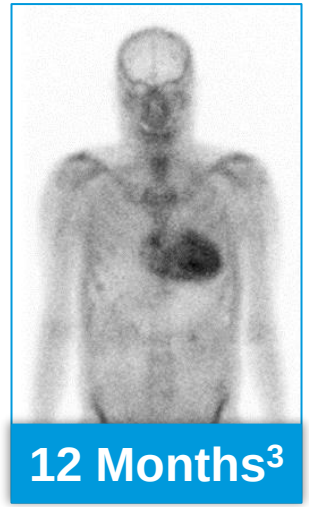
- **55%** Relative reduction in **NT-proBNP** vs. placebo[2,†]
- **0.9mm** Mean reduction in **LV wall thickness** vs. placebo[2,‡]
- **-1.4%** Improvement in **global longitudinal strain** vs. placebo[2,‡]
- **0.35m/s** Improvement in **10-MWT** vs. placebo[2,†]

Investigator-Sponsored Study from National Amyloidosis Centre, UK[3]



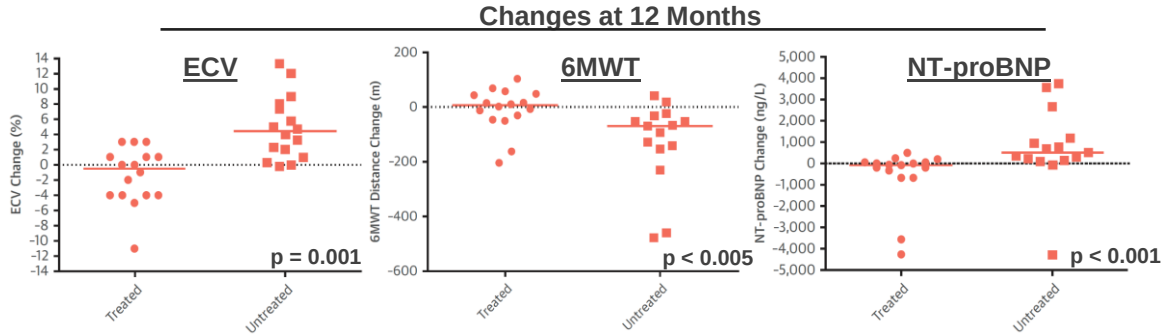
Patient with hATTR and CM, receiving patisiran and diflunisal

Example Tc-DPD Bone Scintigraphy & Image Analysis conducted as part of study, in this patient showing "unequivocal reduction in cardiac and soft tissue uptake"[3]



Cardiac Safety Data in Entire APOLLO Study Population:

	Placebo[5] (n=77)	Patisiran[5] (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 treatment of cardiac amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in treating CM in this population; [2] Solomon S, et al. Circulation 2018;

[3] Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI:10.1016/j.jcmg.2020.07.043; [4] 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; [5] 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

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

Enrollment complete

Topline results expected **mid-2022**

Concomitant use of local standard of care allowed during study, including TTR stabilizer

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

NYHA: New York Heart Association; NT-proBNP: N-terminal pro b-type natriuretic peptide; 6-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

ClinicalTrials.gov Identifier: NCT04153149

1:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Primary Endpoint

- Composite outcome of all-cause mortality and recurrent CV 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

HELIOS·B

HELIOS-B Phase 3 study planned enrollment completion by **late ’21**

Study includes optional interim analysis

Optional HELIOS-B Interim Analysis

Evaluating Options for Potential Readout Before Last Patient Reaches Month 30

- Optional interim analysis included in protocol
  - Details not specified
- Engagement with regulatory authorities to align on a potential approach
- Staging after APOLLO-B data readout in mid ’22
  - Inform finalization of strategy
  - Ensure optimal balance between speed and desired label expansion for vutrisiran in ATTR-CM

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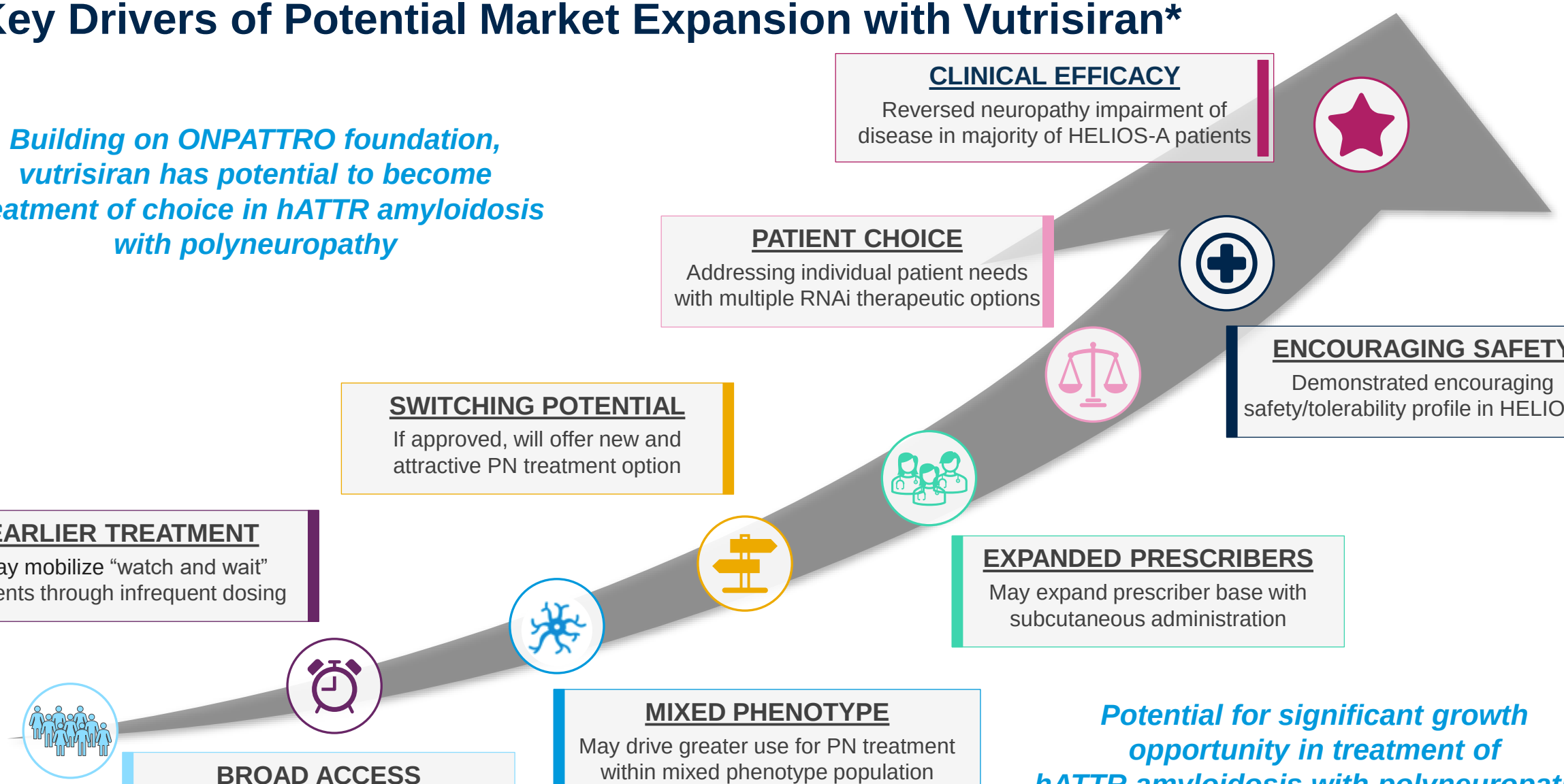
Key Drivers of Potential Market Expansion with Vutrisiran*

Building on ONPATTRO foundation, vutrisiran has potential to become treatment of choice in hATTR amyloidosis with polyneuropathy



CLINICAL EFFICACY
Reversed neuropathy impairment of disease in majority of HELIOS-A patients

PATIENT CHOICE
Addressing individual patient needs with multiple RNAi therapeutic options

ENCOURAGING SAFETY
Demonstrated encouraging safety/tolerability profile in HELIOS-A

SWITCHING POTENTIAL
If approved, will offer new and attractive PN treatment option

EXPANDED PRESCRIBERS
May expand prescriber base with subcutaneous administration

EARLIER TREATMENT
May mobilize "watch and wait" patients through infrequent dosing

MIXED PHENOTYPE
May drive greater use for PN treatment within mixed phenotype population

BROAD ACCESS
Continued innovative approach with payers, ensuring broad access

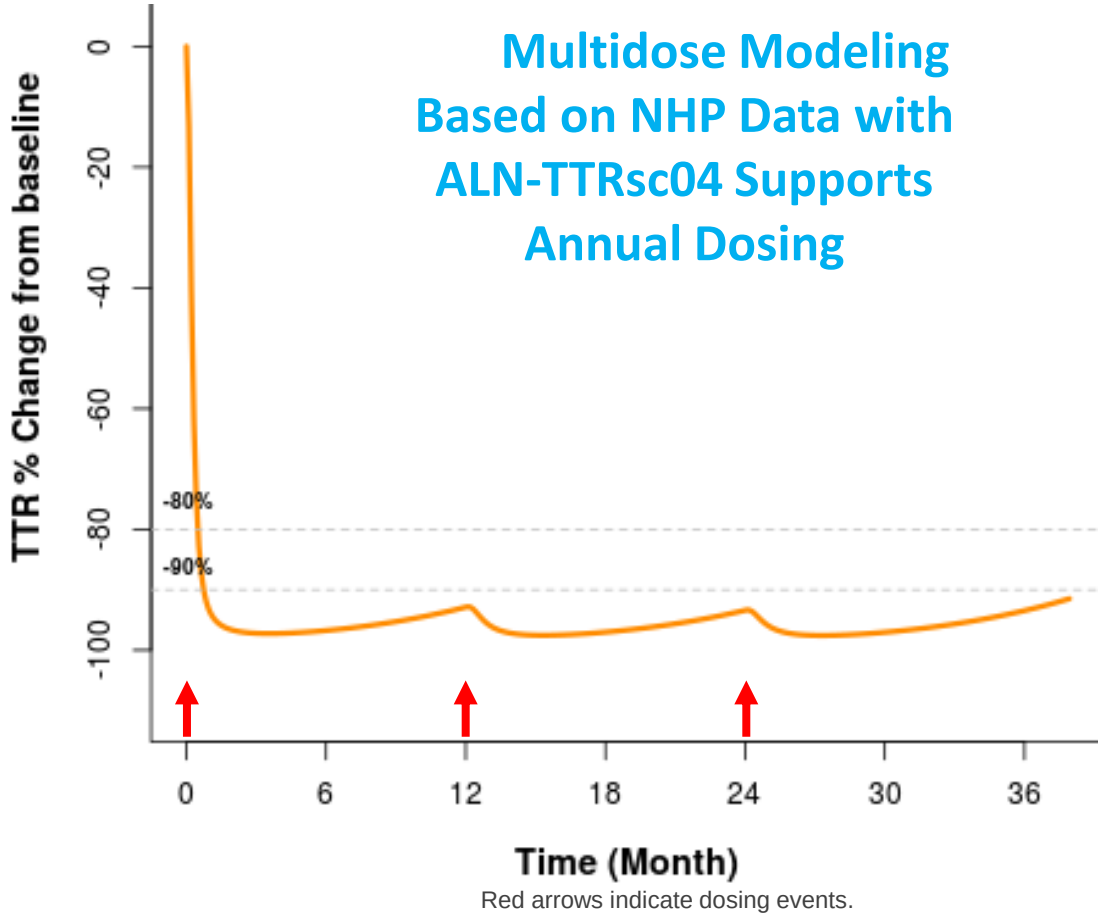
Potential for significant growth opportunity in treatment of hATTR amyloidosis with polyneuropathy based on global approvals of vutrisiran

*Vutrisiran is an investigational RNAi therapeutic, conclusions of safety and effectiveness cannot and should not be drawn; potential market expansion is pending regulatory review and approval as well as other commercial factors

IKARIA™ Platform and Preclinical ALN-TTRsc04

- Continued innovation in RNAi therapeutics
- Extended duration platform with potential for once annual dosing – long-acting and reversible
- Potential for highly potent knockdown (>90%) of target
- Lead IKARIA program: preclinical development with ALN-TTRsc04
- Data to be presented at scientific meeting in mid-'21

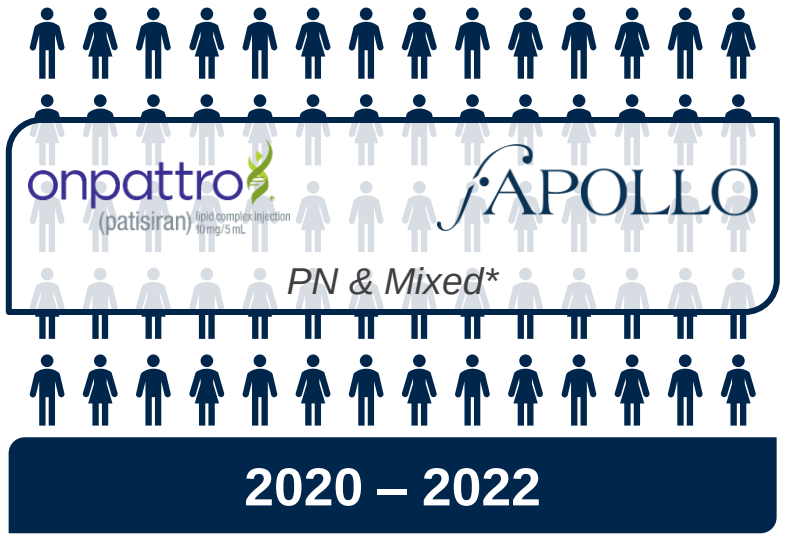
Multidose Modeling Based on NHP Data with ALN-TTRsc04 Supports Annual Dosing

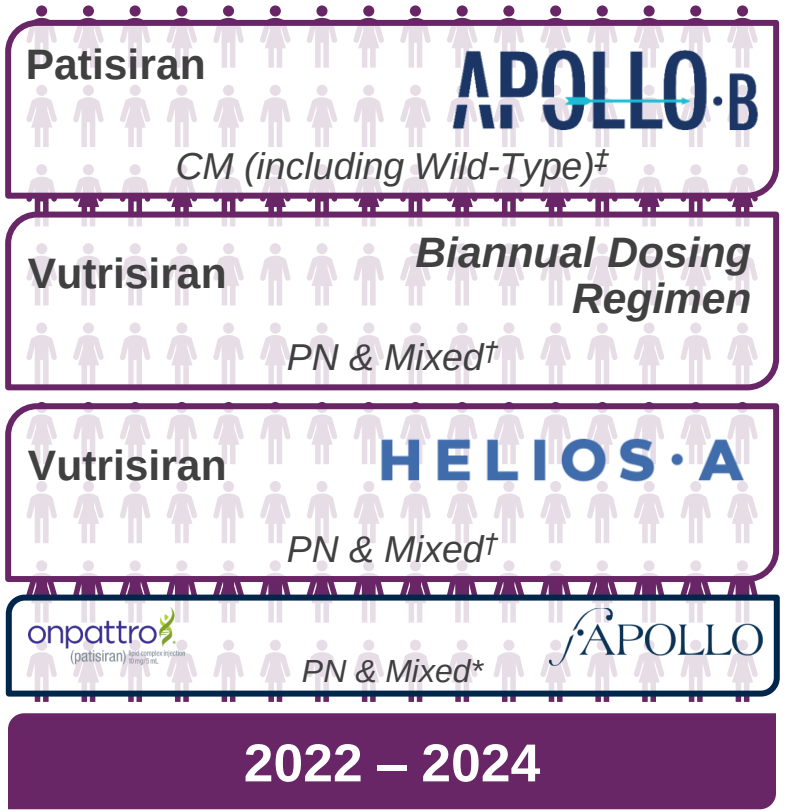


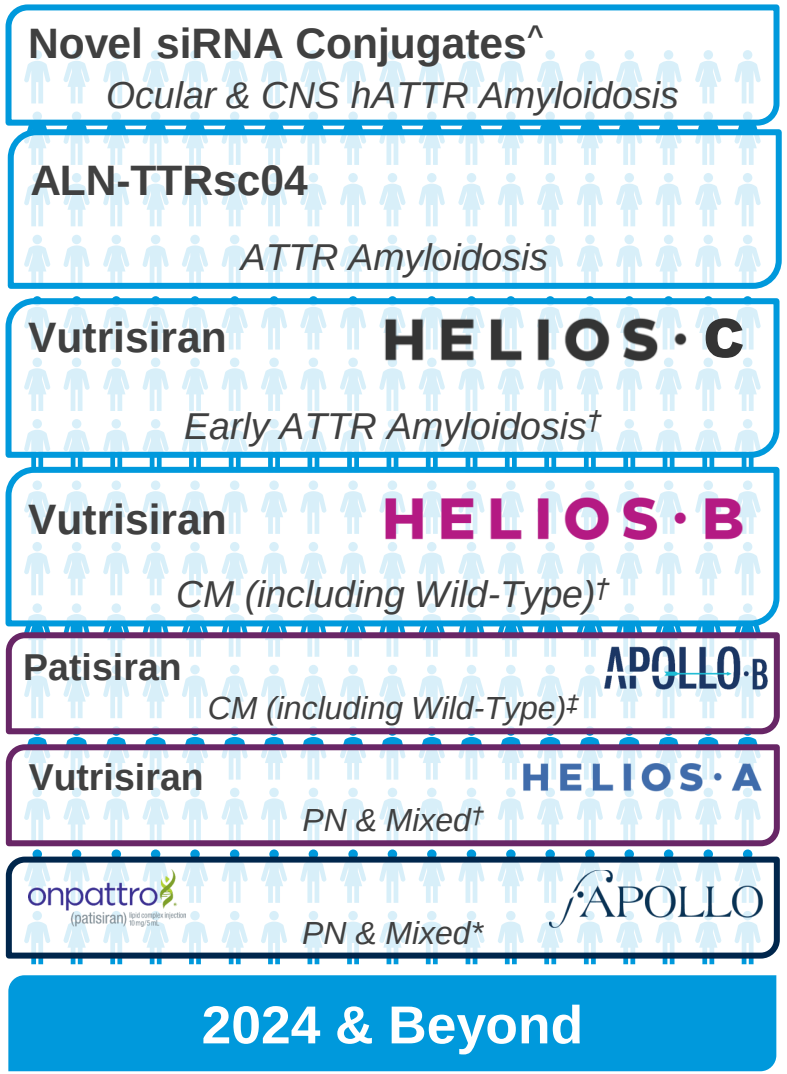
Modeling suggests potential rapid and sustained TTR reduction >90% with annual dosing

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

Building Leading ATTR 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 multiple RNAi therapeutic options to enable patients and physicians to choose the right treatment to address each individual patient's needs

ONPATTRO will remain an attractive option

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

Vutrisiran target profile

Potential to have a highly competitive product profile (efficacy, safety, quarterly and biannual dosing regimen)

Ensure broad access via continued innovation with payers

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Upcoming RNAi Roundtables

Givosiran, for the Treatment of Acute Hepatic Porphyria

- Wednesday, August 4, 1:30 pm ET

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

Alnylam PHARMACEUTICALS