HELIOS-A Phase 3 Study of Vutrisiran

Full 18-Month Results

January 21, 2022

Alnylam@20

Agenda

Welcome
- Christine Lindenboom
  Senior Vice President, Investor Relations & Corporate Communications

Introduction
- Yvonne Greenstreet, MBChB, MBA
  Chief Executive Officer

ATTR Amyloidosis Disease Overview & HELIOS-A 9-Month Results
- Akshay Vaishnaw, M.D., Ph.D.
  President

HELIOS-A 18-Month Results
- Pushkal Garg, M.D.
  Chief Medical Officer and EVP, Development & Medical Affairs

Commercial Preparedness & Next Steps
- Rena Denoncourt
  Vice President, TTR Franchise Lead

Q&A Session

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 "Alnylam P^{5}x25" strategy, the potential expansion of the TTR franchise, the investigational therapeutic vutrisiran and its potential as a low-dose, once quarterly, subcutaneously administered treatment option with an encouraging safety profile for patients living with the polyneuropathy of hATTR amyloidosis, the potential of vutrisiran to treat the cardiac manifestations of disease in patients with ATTR amyloidosis with cardiomyopathy, the ongoing HELIOS-A Phase 3 study, the potential market opportunity in hATTR amyloidosis 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; the potential impact of the recent leadership transition on Alnylam's ability to attract and retain talent and to successfully execute on its "Alnylam P^{5}x25" strategy; 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, including vutrisiran and patisiran; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including vutrisiran, 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 (and vutrisiran, if approved) 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, Regeneron and Vir; the outcome of litigation; the potential impact of a current government investigation and the 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 Annual Report on Form 10-K 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.

Yvonne Greenstreet, MBChB, MBA

Chief Executive Officer

Introduction

Alnylam TTR Franchise

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

2020 – 2022

Patisiran — APOLLO-B
ATTR Amyloidosis with CM (incl. WT)‡

Vutrisiran — ***Biannual Dosing Regimen***
hATTR Amyloidosis with PN & Mixed†

Vutrisiran — HELIOS-A
hATTR Amyloidosis with PN & Mixed†

onpattro (patisiran) — APOLLO
*hATTR Amyloidosis with PN & Mixed**

2022 – 2024

Novel siRNA Conjugates^
Ocular & CNS hATTR Amyloidosis

ALN-TTRsc04
ATTR Amyloidosis

Vutrisiran — HELIOS-C
Early ATTR Amyloidosis†

Vutrisiran — **Phase 3**
Stargardt Disease

Vutrisiran — HELIOS-B
ATTR Amyloidosis with CM (incl. WT)†

Patisiran — APOLLO-B
ATTR Amyloidosis with CM (incl. WT)‡

Vutrisiran — HELIOS-A
hATTR Amyloidosis with PN & Mixed†

onpattro (patisiran) — APOLLO
*hATTR Amyloidosis with PN & Mixed**

2024 & Beyond

* 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 hATTR or ATTR 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

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

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

President

ATTR Amyloidosis Disease Overview

Catalania (Spain)
Diagnosed with hATTR amyloidosis

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

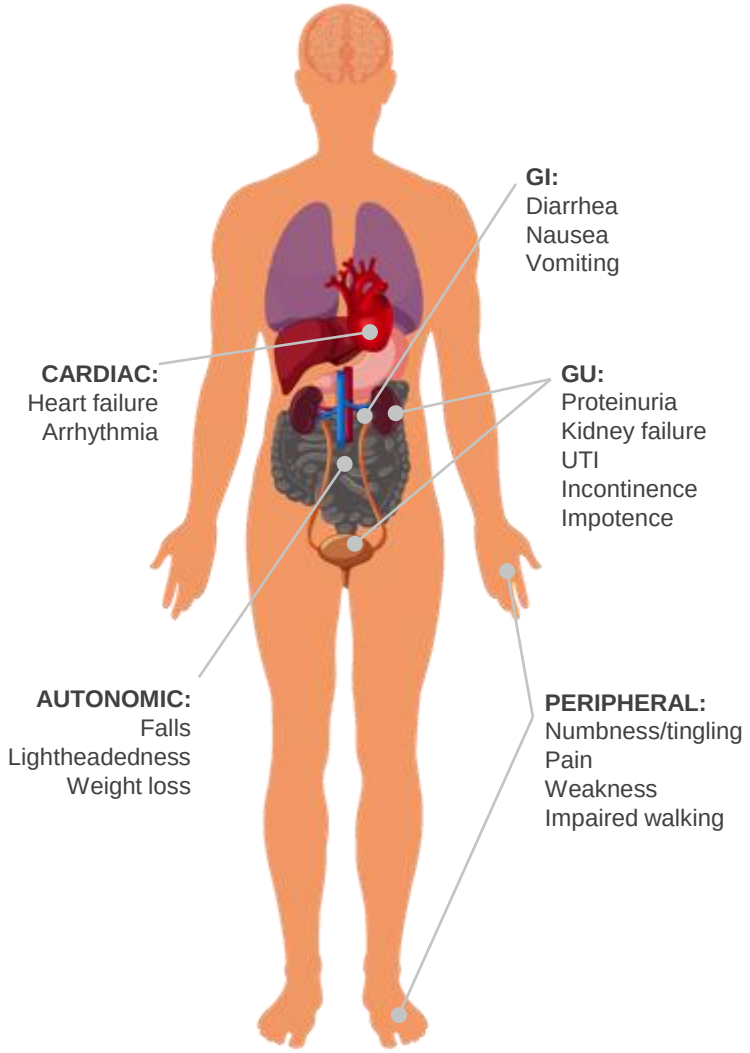
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

patients worldwide

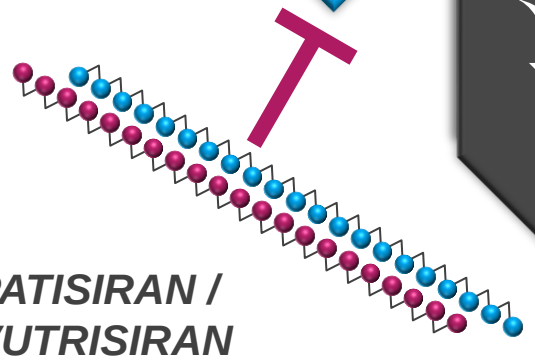


[1] Coelho T, et al. N Engl J Med. 2013;369(9):819-829

* Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012 (includes hATTR amyloidosis patients with polyneuropathy and cardiomyopathy)

RNAi Therapeutic Hypothesis in ATTR Amyloidosis

Silencing TTR Gene Expression Can Potentially Address Underlying Cause of Disease



PATISIRAN / VUTRISIRAN

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

Production of variant and wild-type TTR in liver*

Reduce
circulating TTR

Prevent or clear
tissue amyloid deposits

Halt or improve
progressive manifestations of disease

* >95% of TTR in circulation produced in liver

Alnylam's 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 with CM ‡
- 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 with PN
- HELIOS-B ongoing in ATTR with CM
- Subcutaneous administration, once quarterly, potential for biannual dosing

ALN-TTRsc04

A Preclinical RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis

About ALN-TTRsc04

- IKARIA platform
- IND expected in 2022
- Potential for annual dosing and >90% serum TTR reduction
- No third-party royalties; exclusivity expected 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

Pushkal Garg, M.D.

Chief Medical Officer and EVP, Development & Medical Affairs

HELIOS-A 18-Month Results

Vutrisiran HELIOS·A Phase 3 Study

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

HELIOS·A

- As previously reported, the primary endpoint of change from baseline in mNIS+7 at Month 9 was met[1]

Patient Population N=164

- 18–85 years old
- hATTR amyloidosis with polyneuropathy; any *TTR* mutation
- NIS 5–130 and PND ≤IIIB
- KPS ≥60%
- Prior tetramer stabilizer use permitted

3:1 RANDOMIZATION

Stratification:
TTR V30M vs non-V30M
Baseline NIS <50 vs ≥50

n=122
Vutrisiran
25 mg
SC Q3M

or

n=42
Reference comparator
(patisiran)
0.3 mg/kg
IV Q3W

Efficacy Assessments

Vutrisiran vs APOLLO Placebo

Primary Endpoint (at Month 9; previously presented[1])
- Change from baseline in mNIS+7[a]

Secondary Endpoints
Change from baseline in:
- mNIS+7 at Month 18
- Norfolk QOL-DN[b] at Months 9 and 18
- 10-MWT[c] at Months 9 and 18
- mBMI[d] at Month 18
- R-ODS[e] at Month 18

Selected Exploratory Endpoints
- Change from baseline in cardiac biomarkers, echocardiographic parameters to Month 18
- Change from baseline in Tc scintigraphy measures to Month 18[f]

Vutrisiran vs HELIOS-A Patisiran

Secondary Endpoint
- % serum TTR reduction to Month 18

[a]Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304). [b]Higher scores of Norfolk QOL-DN indicate worse quality of life (range, −4 to 136). [c]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. [d]Lower scores of mBMI ([weight in kg/m^2] x serum albumin g/L) indicate worse nutritional status. [e]Lower scores of R-ODS indicate more disability (range, 0 to 48). [f]Tc scintigraphy was only performed at select sites, comparison to baseline, not placebo

10-MWT, 10-meter walk test; ATTRv, transthyretin-mediated amyloidosis (v for variant); hATTR, hereditary transthyretin-mediated amyloidosis; 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; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; Tc, technetium; TTR, transthyretin.

1. Adams D et al. *Neurology* 2021;96(15 Supplement):1234.

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)
Previous tetramer stabilizer use, n (%)	41 (53.2)	75 (61.5)	33 (78.6)
PND score,[a] 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 (%)[b,c]	36 (47)	40 (33)	14 (33)

[a]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). [b]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). [c]Select echocardiogram parameters were re-read for the Month 18 analysis and the cardiac subpopulation was re-derived based on baseline LV wall thickness values after the re-read. As a result, in the Month 18 analysis the cardiac subpopulation status of 9 patients receiving vutrisiran was reclassified and 1 patient receiving patisiran was added to the cardiac subpopulation compared with the cardiac subpopulation defined in the Month 9 analysis.

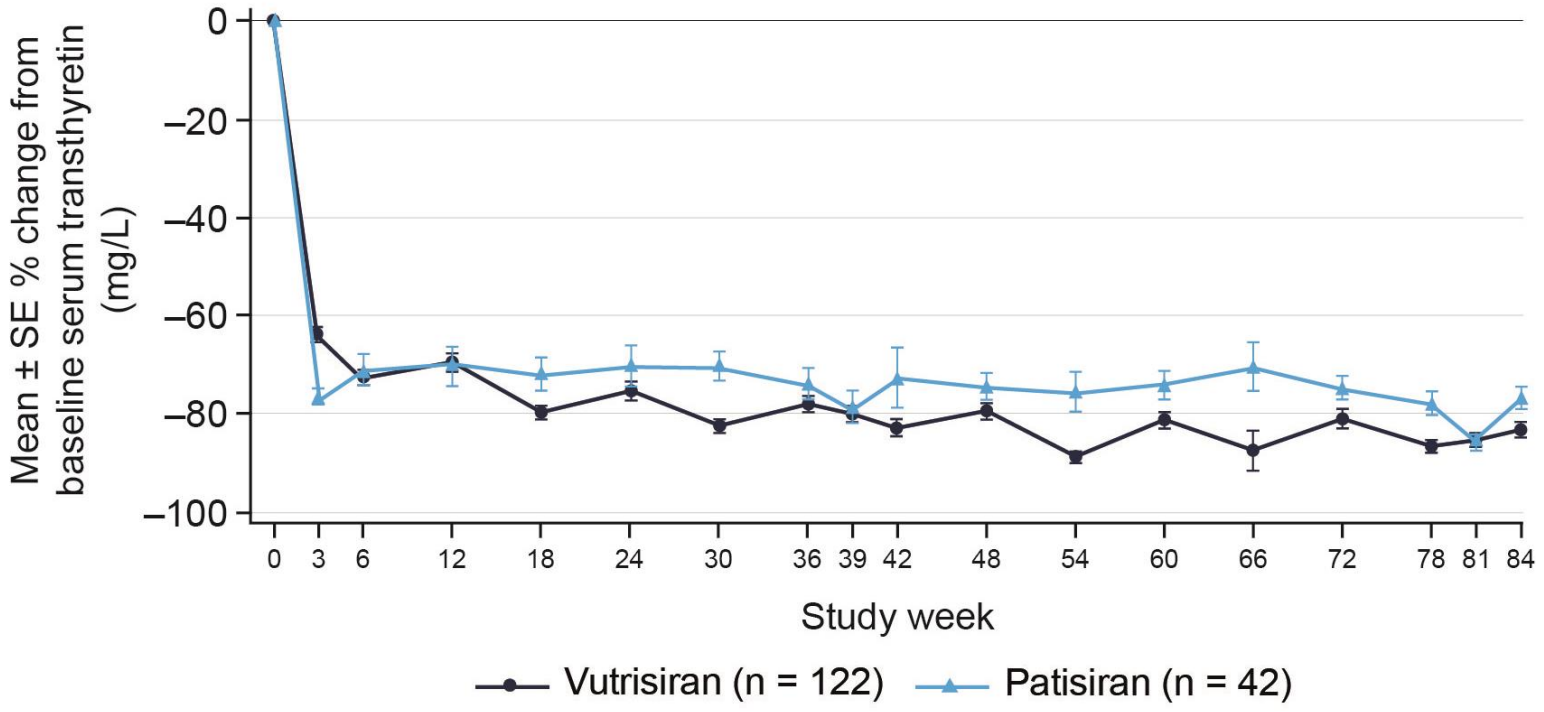
NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; TTR, transthyretin.

Adams, et al. SFNP 2022

Rapid and Sustained Reduction in Serum TTR Levels with Vutrisiran

- Vutrisiran achieved a mean steady-state serum TTR reduction from baseline of 88% (SD: 16%)
- TTR reduction with vutrisiran was non-inferior to that observed with the within-study patisiran reference comparator (secondary endpoint) over 18 months[a]

Percent Change from Baseline in Serum TTR Levels



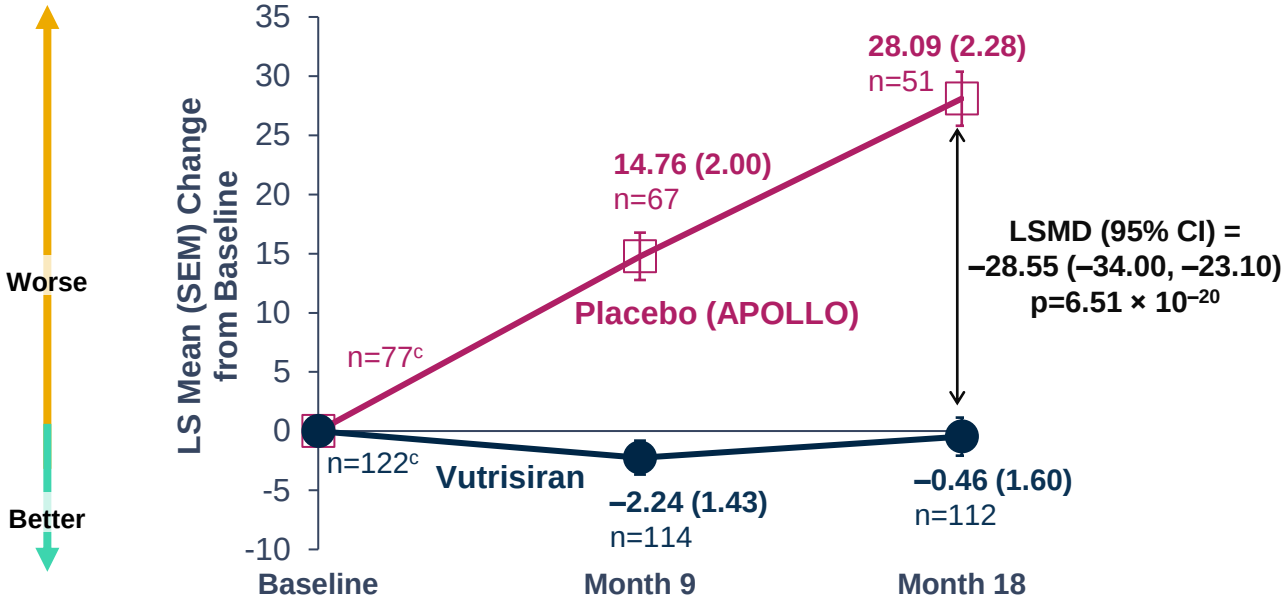
N evaluable																		
Vutrisiran (n = 122)	122	114	109	119	106	117	92	118	115	56	116	42	118	15	118	100	114	98
Patisiran (n = 42)	42	42	41	41	37	38	39	34	39	23	40	23	36	9	37	36	38	32

[a]As assessed by mean trough serum TTR levels; SD, standard deviation; SE, standard error; TTR, transthyretin; Adams, et al. SFNP 2022

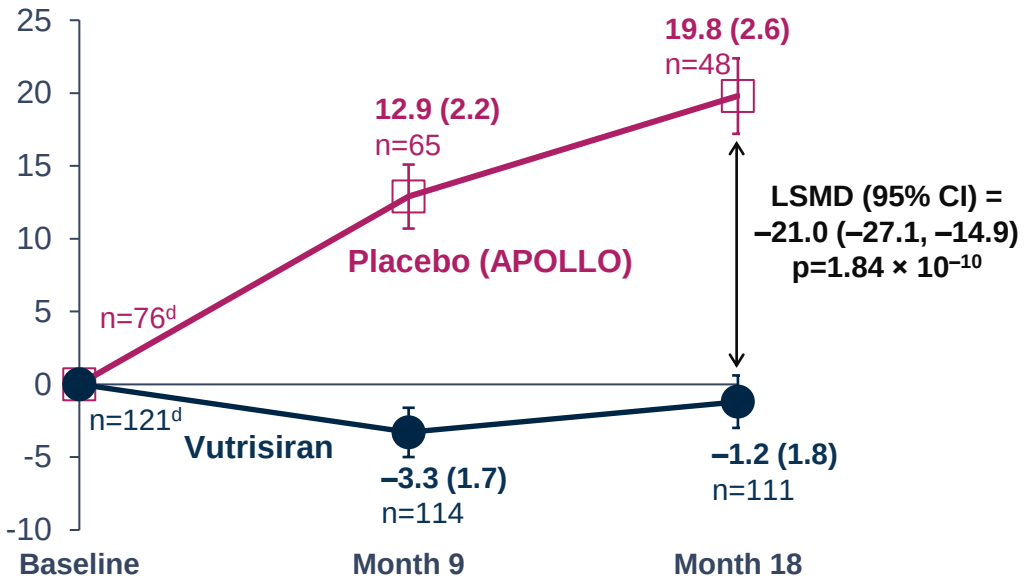
Statistically Significant Improvement in Neuropathy Impairment and Quality of Life with Vutrisiran vs External Placebo at Month 18

- Improvement was observed across all prespecified patient subgroups, components, and subdomains of mNIS+7 and Norfolk QOL-DN (data not shown)
- Improvement relative to baseline[a] in mNIS+7 (48.3% [vutrisiran] vs 3.9% [placebo]) and Norfolk QOL-DN (56.8% vs 10.4%)
- Consistent treatment effects in vutrisiran and patisiran groups in HELIOS-A (data not shown)

mNIS+7 LS Mean Change from Baseline[b]



Norfolk QOL-DN LS Mean Change from Baseline[b]

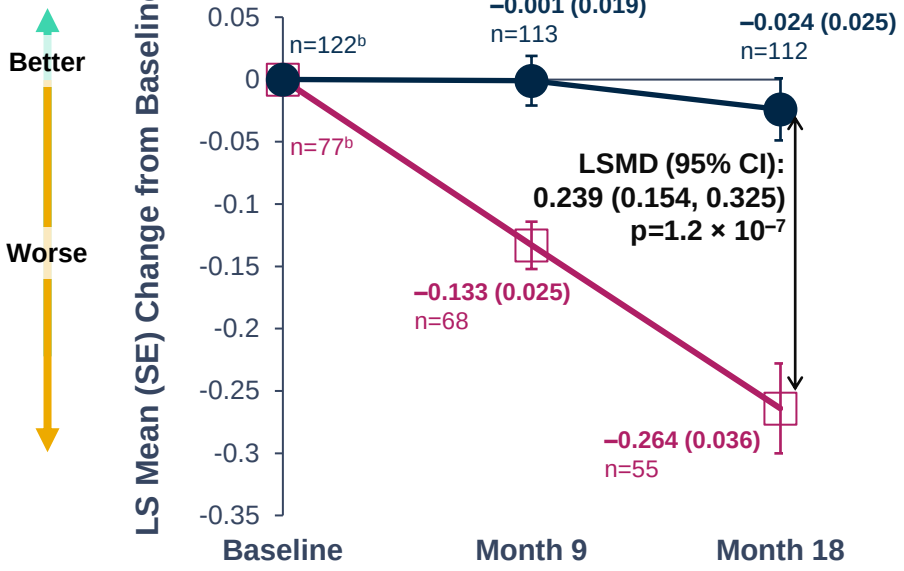


[a]Improvement defined as patients with <0-point increase from baseline to 18 months. [b]mITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Data plotted for mNIS+7 and Norfolk QOL-DN at Month 9 are ANCOVA/multiple imputation model data and data plotted at Month 18 are MMRM model data. **[c]At baseline, the mean (±SD) mNIS+7 was 60.6 (36.0) in the vutrisiran group and 74.6 (37.0) in the external placebo group. [d]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.**

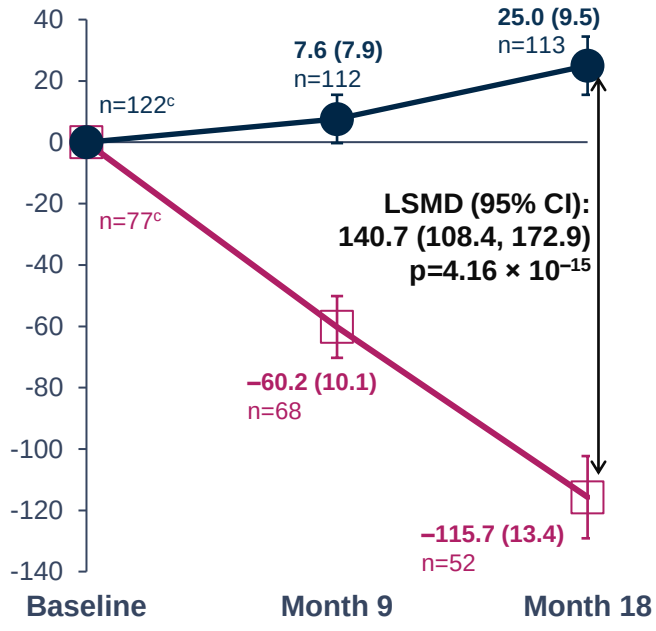
ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SD, standard deviation; SEM, standard error of the mean. Adams, et al. SFNP 2022

Statistically Significant Improvement in Secondary Endpoints with Vutrisiran vs External Placebo at Month 18

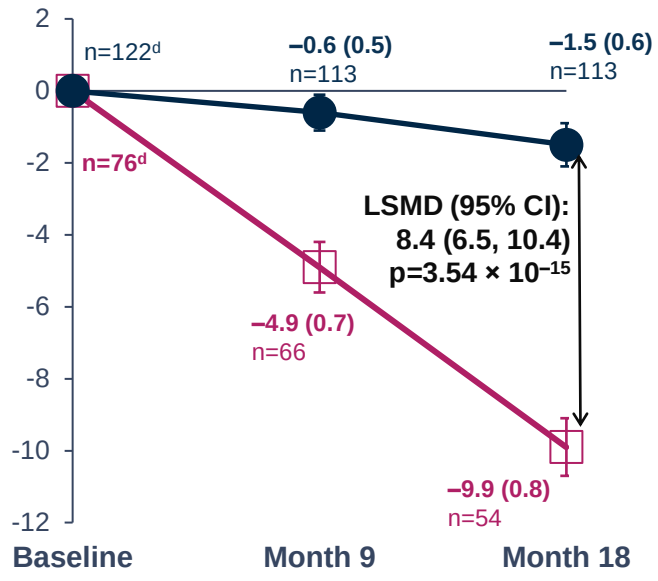
10-MWT (Gait Speed) LS Mean Change from Baseline[a]



mBMI (Nutritional Status) LS Mean Change from Baseline[a]



R-ODS (Disability) LS Mean Change from Baseline[a]



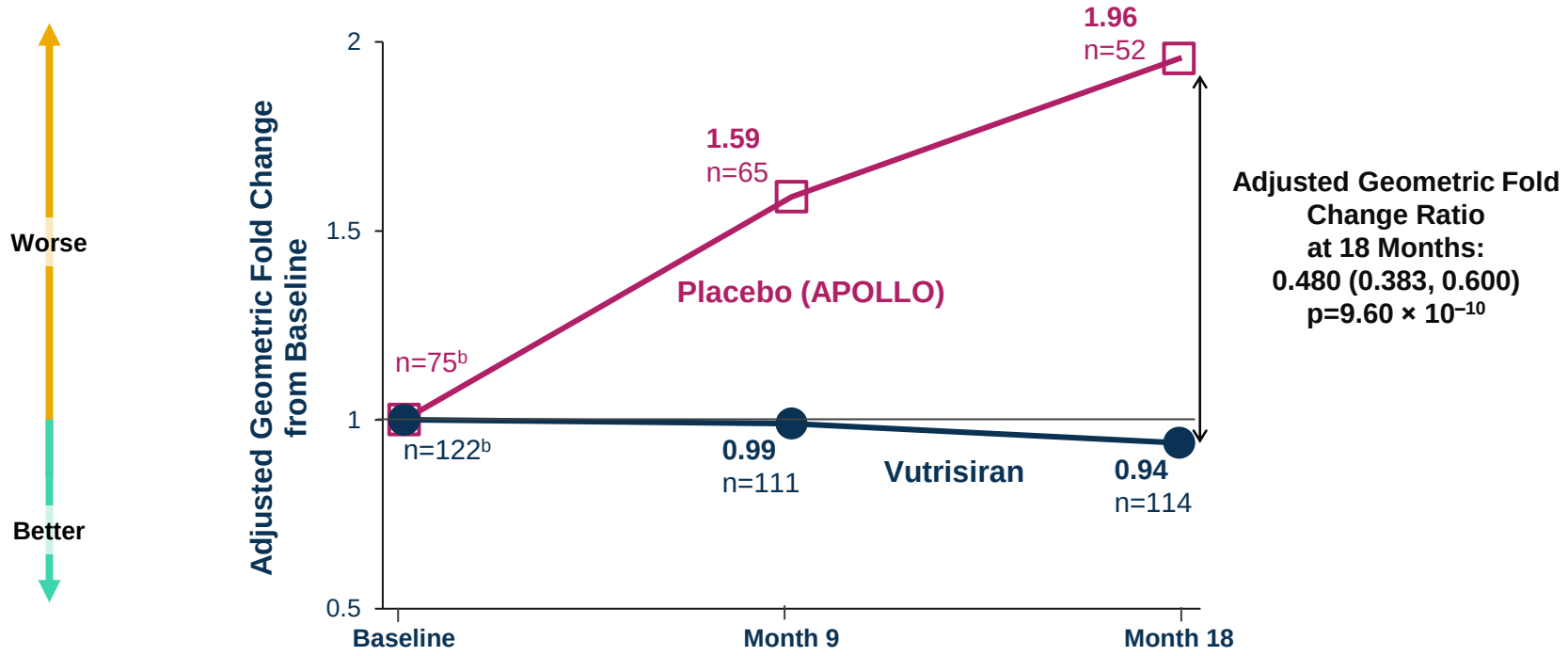
Placebo (APOLLO) Vutrisiran

[a]mITT population (all randomized patients who received any amount of study drug) for all endpoints. Value of n is the number of evaluable patients at each timepoint. Data plotted for 10-MWT, mBMI and R-ODS at Month 9 are ANCOVA/multiple imputation model data and data plotted at Month 18 are MMRM model data. [b]**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**. [c]**At baseline, the mean (±SD) mBMI was 1057.4 (233.8) in the vutrisiran group and 989.9 (214.2) in the external placebo group**. [d]**At baseline, the mean (±SD) R-ODS was 34.1 (11.0) in the vutrisiran group and 29.8 (10.8) in the external placebo group**.

10-MWT, 10-meter walk test; ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; LSMD, LS mean difference; mBMI, modified body mass index; mITT, modified intent-to-treat; MMRM, mixed model repeated measures; R-ODS, Rasch-built Overall Disability Scale; SD, standard deviation; SE, standard error. Adams, et al. SFNP 2022

Improvement in Exploratory Assessment of NT-proBNP with Vutrisiran vs External Placebo at Month 18

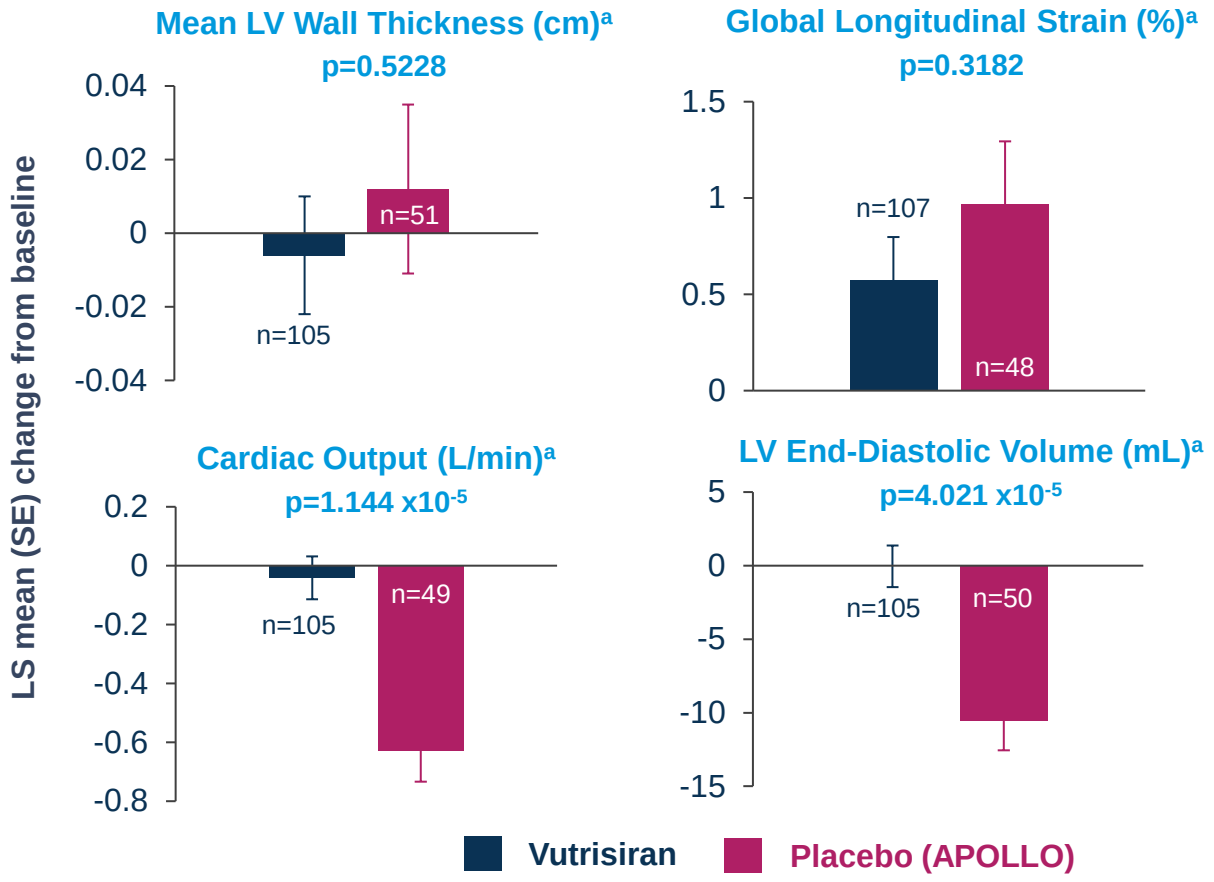
Change from Baseline in NT-proBNP (mITT Population)[a]



[a]NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. [b]**At baseline, NT-proBNP geometric mean (SE) was 273.0 (42.2) ng/L in the vutrisiran group (n=122) and 531.3 (86.7) ng/L in the APOLLO placebo group (n=75).** Number of evaluable patients at each timepoint are shown. Data plotted for NT-proBNP at Month 9 are ANCOVA/multiple imputation model data and data plotted at Month 18 are MMRM model data.
ANCOVA, analysis of covariance; mITT, modified intent-to-treat; MMRM, mixed model repeated measures; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; SE, standard error. Adams, et al. SFNP 2022

Vutrisiran Shows Encouraging Trend in Exploratory Echocardiographic Parameters

- Echocardiographic parameters represent an exploratory assessment of cardiac structure and function
- Vutrisiran trended toward improvement in all echocardiographic parameters, compared with external placebo group

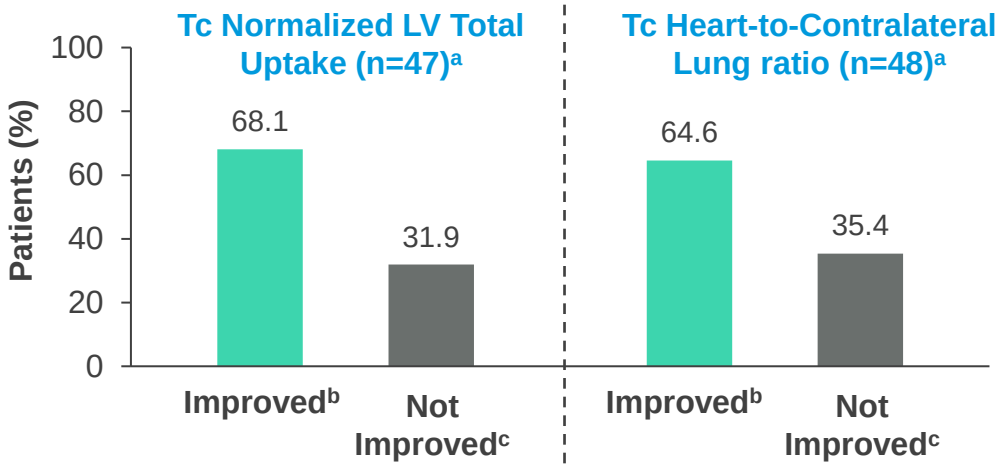


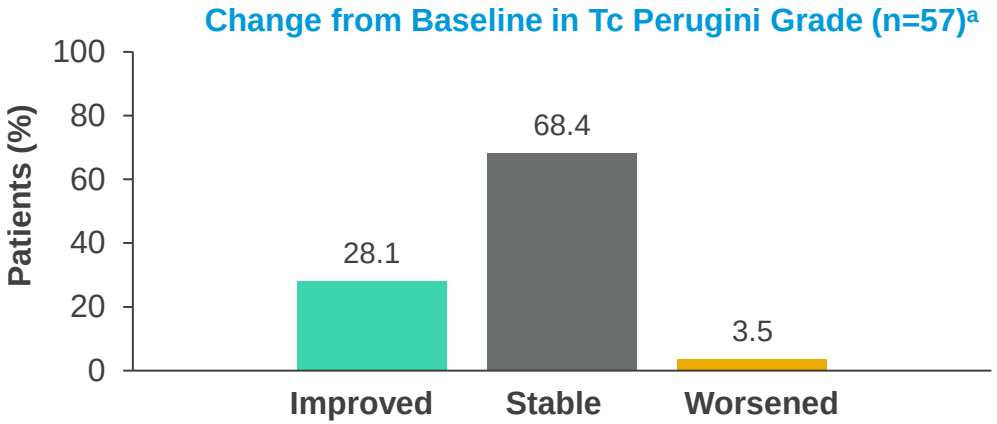
[a]mITT population. P-values are nominal. Adams, et al. SFNP 2022

Reduced Cardiac Technetium Uptake on Scintigraphy Imaging Shown in Majority of Assessable Vutrisiran Patients

Potential Evidence of Reduction in Amyloid Burden

- HELIOS-A Tc Scintigraphy imaging in planned cohort
  - Conducted at baseline and Month 18, at select sites
  - Assessment of improvement relative to individual patient's baseline
- Tc scintigraphy: non-invasive assessment of cardiac amyloid involvement
  - Quantitatively assessed by normalizing uptake in heart to contralateral lung (heart-to-contralateral lung ratio), or to total amount of radio-tracer administered (normalized LV uptake)
  - Perugini grading assesses Tc uptake in myocardium compared to bones; widely used in diagnosis of ATTR amyloidosis





[a]Patients from the mITT population for whom the relevant 18 month data were available. [b]Improved: <0 increase from baseline. [c]Not improved: ≥0 increase from baseline. mITT, modified intent-to-treat; SE, standard error; Tc, technetium. Adams, et al. SFNP 2022

Month 18 HELIOS-A Vutrisiran Results Recapitulate Efficacy Seen with APOLLO Patisiran Across Primary, Secondary and Exploratory Measures

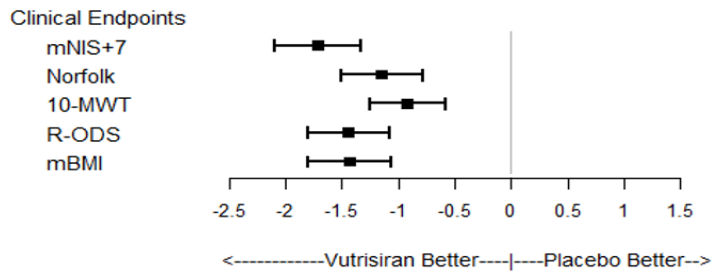
Findings Consistent with Similar Serum TTR Reduction Seen with Vutrisiran and Patisiran

Primary and Secondary PN Endpoints

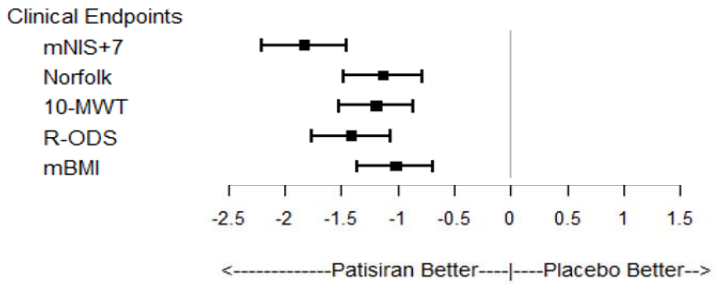
mITT^

Standardized Effect Sizes

HELIOS-A (Vutrisiran)



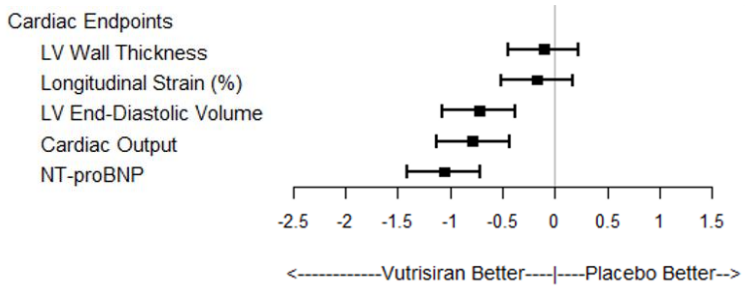
APOLLO (Patisiran)

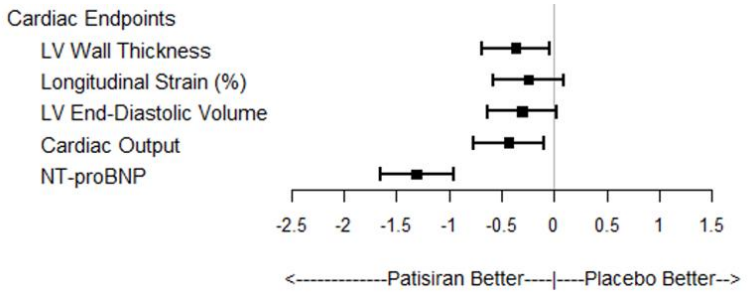


Exploratory CM Endpoints*

mITT^

Standardized Effect Sizes

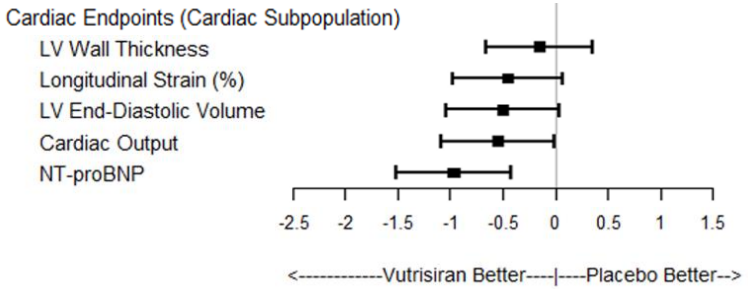


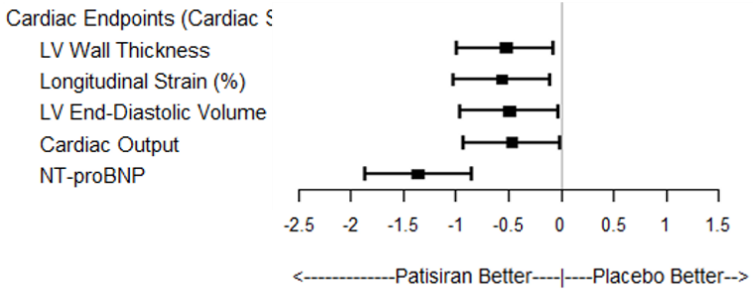


Exploratory CM Endpoints*

Cardiac Subpopulation

Standardized Effect Sizes





*Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for treatment of ATTR amyloidosis with CM. No conclusions can or should be drawn regarding its safety or effectiveness in treating CM in this population;
^Adams, et al. SFNP 2022

HELIOS-A Safety Summary[a]

Majority of AEs mild or moderate in severity

- No drug-related discontinuations or deaths
- Three study discontinuations (2.5%) due to AEs in the vutrisiran arm (two due to death, as previously reported; one due to heart failure), none of which were considered related to study drug
  - One death due to COVID-19 pneumonia and the other due to iliac artery occlusion
- As previously reported, two SAEs deemed related to vutrisiran by investigators:
  - Dyslipidemia and urinary tract infection
- AEs ≥10% in the vutrisiran group included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness
- Injection-site reactions were reported in 5 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[a]

	APOLLO	HELIOS-A	
At least one event, n (%)	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
AEs	75 (97.4)	119 (97.5)	41 (97.6)
SAEs	31 (40.3)	32 (26.2)	18 (42.9)
Severe AEs	28 (36.4)	19 (15.6)	16 (38.1)
AEs leading to treatment discontinuation	11 (14.3)	3 (2.5)	3 (7.1)
AEs leading to stopping study participation	9 (11.7)	3 (2.5)	2 (4.8)
Deaths	6 (7.8)	2 (1.6)	3 (7.1)

[a]Data reported during 18-month treatment period.

AE, adverse event; SAE, serious AE. Adams, et al. SFNP 2022

HELIOS-A Month 18 Data Summary

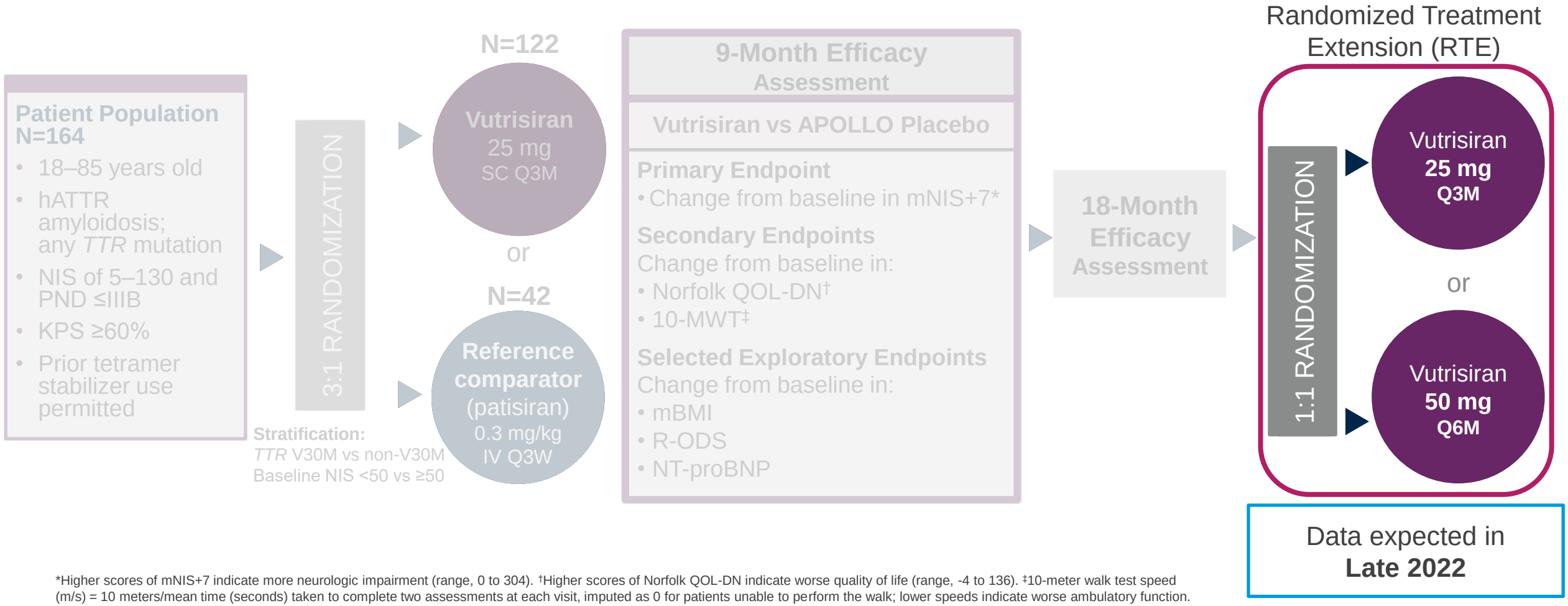
- As previously reported, vutrisiran met the HELIOS-A primary endpoint (mNIS+7) at 9 months
- Vutrisiran met all 18-month secondary endpoints
  - Maintained statistically significant improvement in mNIS+7 compared with external placebo
  - Improvement in QOL (Norfolk QOL-DN), gait speed (10-MWT), nutritional status (mBMI) and disability (R-ODS), compared with external placebo
  - Robust and sustained TTR reduction, non-inferior to within-study patisiran
- Exploratory endpoints suggest potential beneficial effect on cardiac manifestations
- Vutrisiran had an acceptable safety profile
- HELIOS-A continues to investigate efficacy and safety of vutrisiran in hATTR patients with polyneuropathy through ongoing extension period

10-MWT, 10-meter walk test; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; QOL, quality of life; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin.

1. Adams D et al. *Neurology* 2021;96(15 Supplement):1234. Adams, et al. SFNP 2022

Vutrisiran HELIOS·A Phase 3 Study

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

Rena Denoncourt

Vice President, TTR Franchise Lead

Commercial Preparedness & Next Steps

hATTR Amyloidosis Market Opportunity

Estimated Disease Prevalence*†

~ 50,000 patients worldwide

NEUROLOGIC PHENOTYPE
> 50% have cardiomyopathy

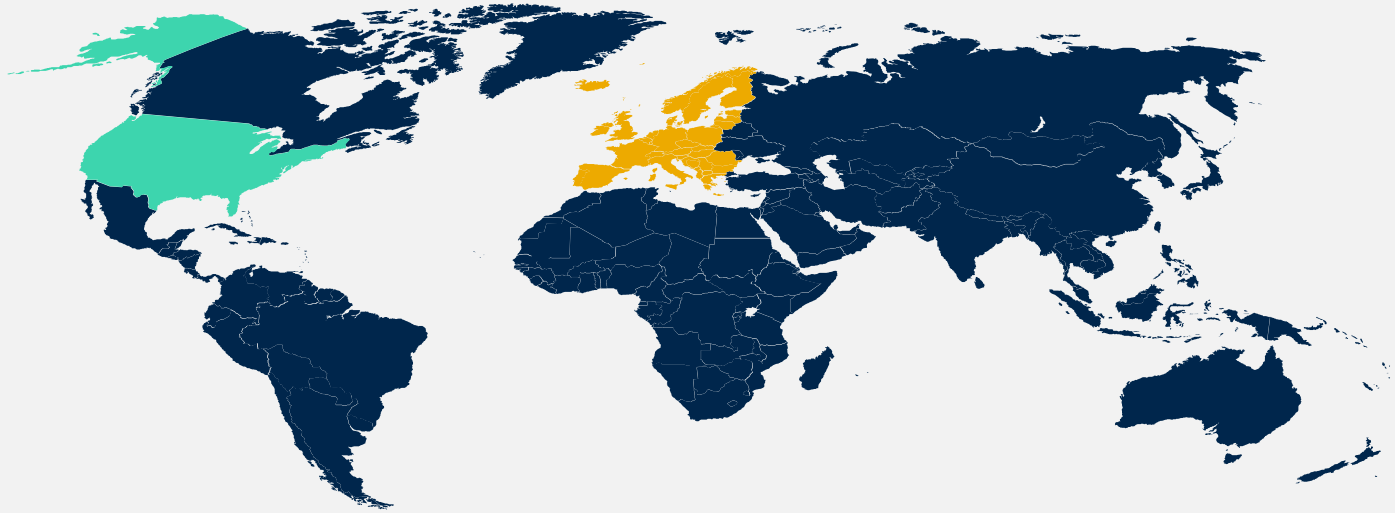
CARDIAC PHENOTYPE†
> 50% have neuropathy

PN & MIXED†

20K to 30K worldwide
~ 10K diagnosed‡

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

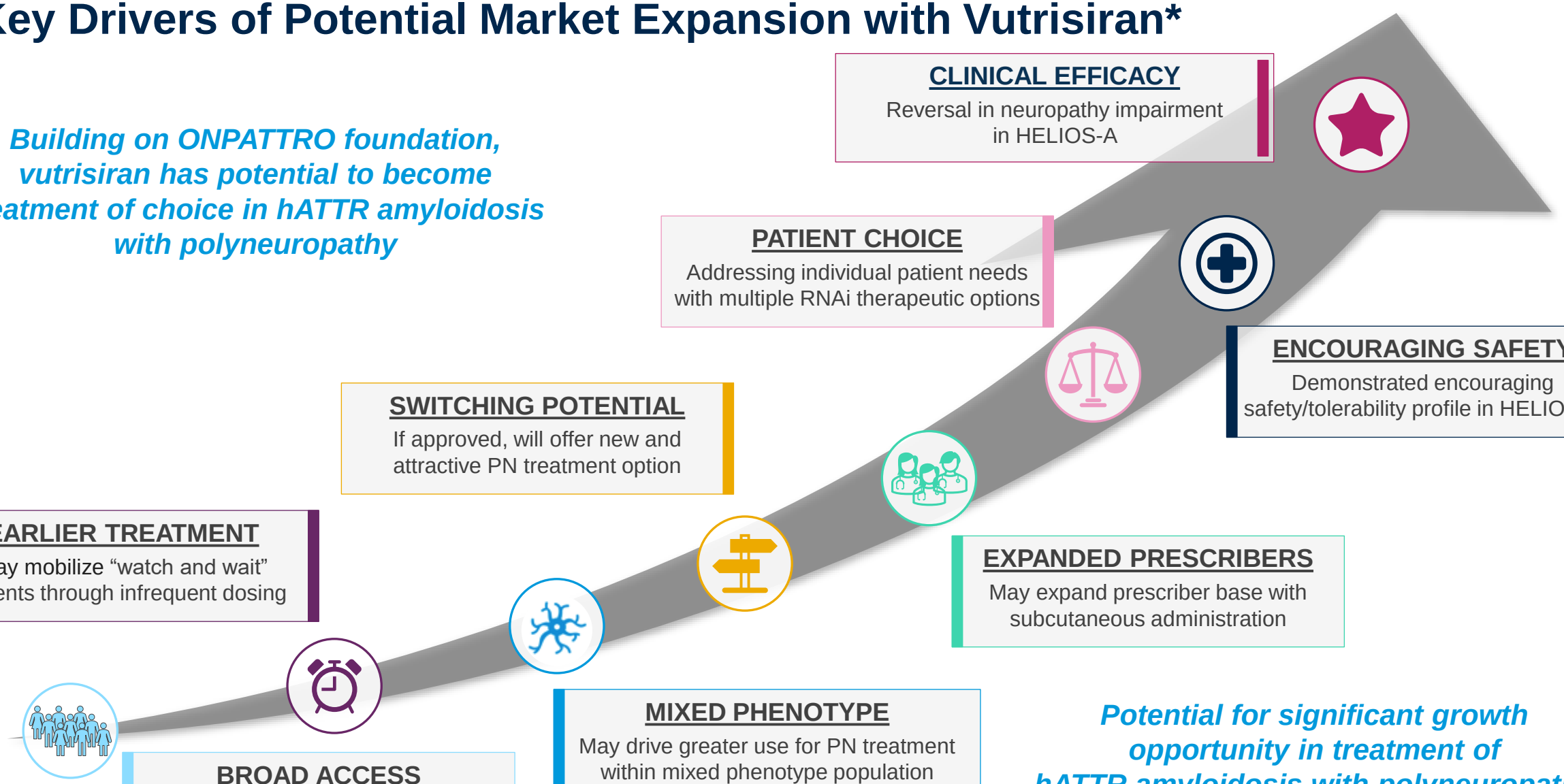
5K to 10K in EU
~ 2K diagnosed



* Based on Alnylam estimates from interviews with key opinion leaders, THAOS registry, recent clinical trials and literature
† ONPATTRO is approved in 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. ONPATTRO has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis.
† 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 to treat patients with polyneuropathy or cardiomyopathy
‡ Current diagnosis rates difficult to confirm and may be lower in initial launch years

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
Reversal in neuropathy impairment in HELIOS-A

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

HELIOS-A 18-Month Results

Q&A Session