Conference Call to Discuss FDA Approval of AMVUTTRA™ (vutrisiran)

June 14, 2022

Alnylam®@20

Agenda

Welcome

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

Introduction

- Yvonne Greenstreet, MBChB, MBA
  Chief Executive Officer

ATTR Amyloidosis Overview

- Akshay Vaishnaw, M.D., Ph.D
  President

AMVUTTRA™ (vutrisiran) Label & Data

- Pushkal Garg, M.D.
  Chief Medical Officer

Commercialization Strategy

- Tolga Tanguler
  Chief Commercial Officer

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 aspiration to become a leading biotech company and the planned achievement of our "*Alnylam P^{5}x25*" strategy, our ability to attain financial self-sustainability, the drivers of our future growth potential, including the potential of our TTR franchise and the launch of AMVUTTRA for the treatment of the polyneuropathy of hATTR amyloidosis in the U.S. and, if approved by other regulatory authorities, in additional territories, the potential for investigational RNAi therapeutics in ATTR cardiomyopathy, the potential market opportunity for AMVUTTRA for the treatment of hATTR amyloidosis patients with polyneuropathy, and the key drivers for potential market expansion for AMVUTTRA. 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 our ability to attract and retain talent and to successfully execute on our "*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 OXLUMO, ONPATTRO and AMVUTTRA 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.

Yvonne Greenstreet, MBChB, MBA

Introduction

CELEBRATING 20 YEARS OF ALNYLAM LEADERSHIP AND WHAT'S NEXT IN THE RNAi Revolution

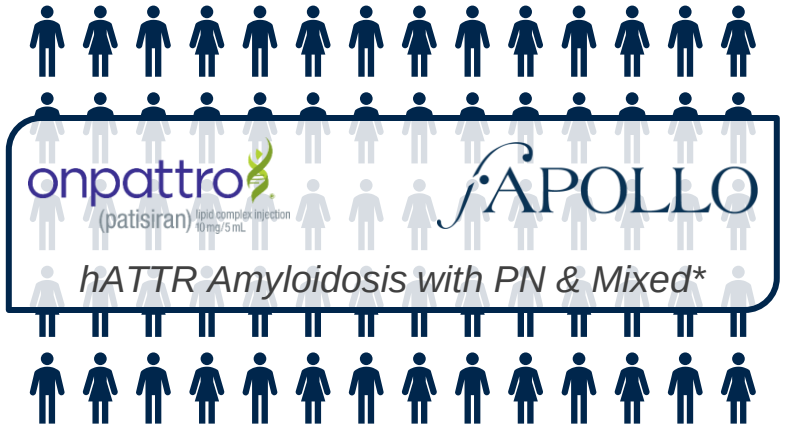
The fifth RNAi therapeutic is

NOW APPROVED

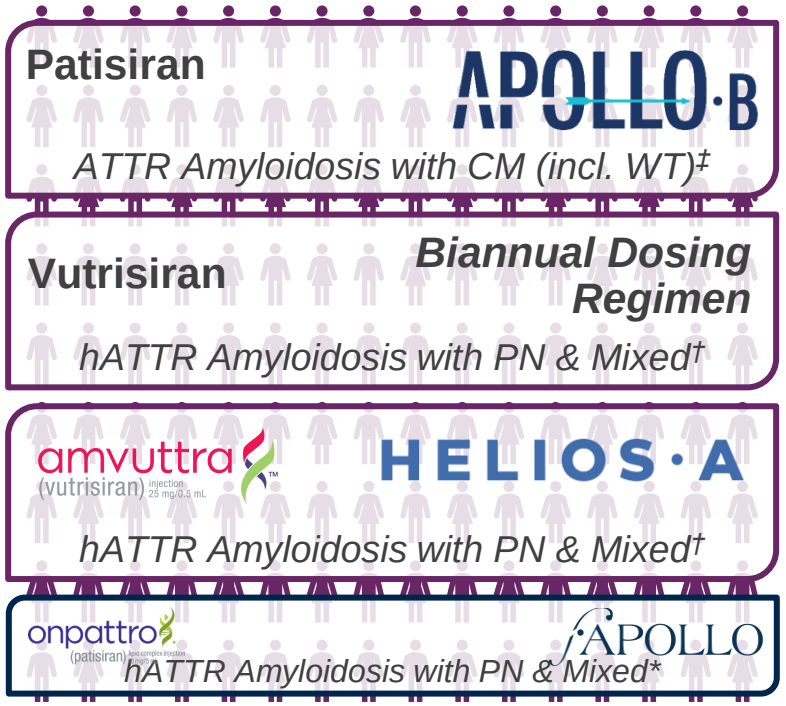
amvuttra™
(vutrisiran) injection
25 mg/0.5 mL

Alnylam TTR Franchise

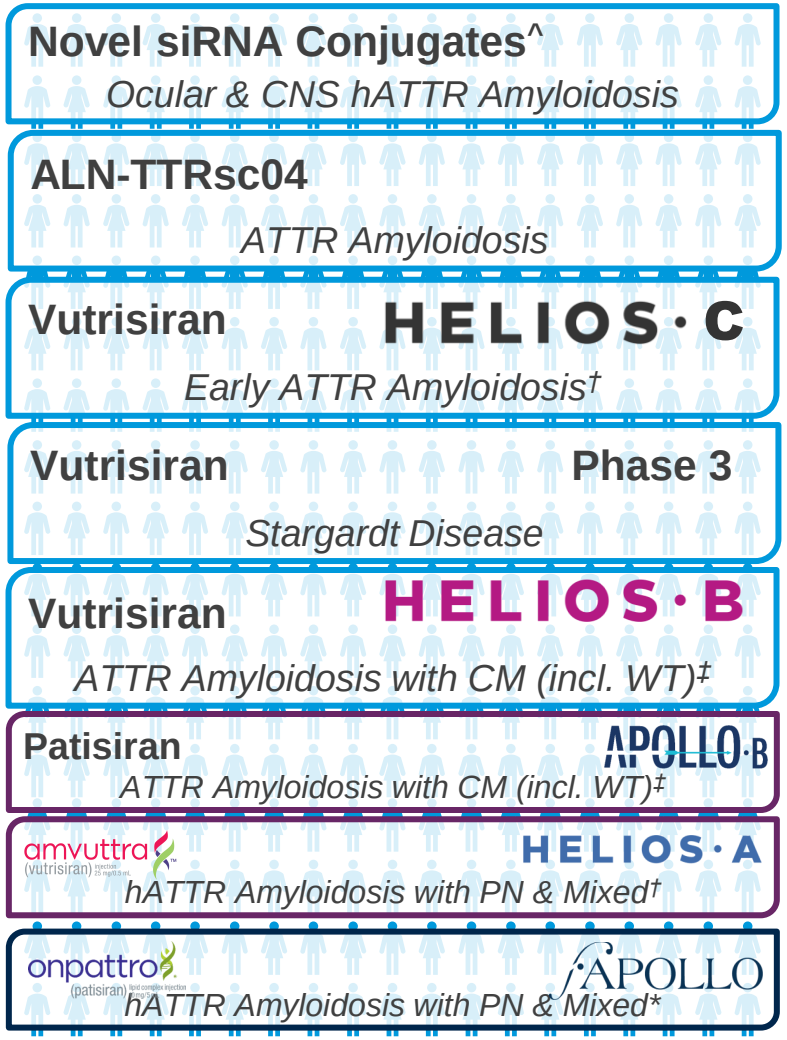
Potential to Expand Value to Patients Globally for Many Years to Come



2020 – 2022



2022 – 2024



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 and AMVUTTRA have 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

† AMVUTTRA is approved in the U.S. for the treatment of the PN of hATTR amyloidosis in adults; ^ 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 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

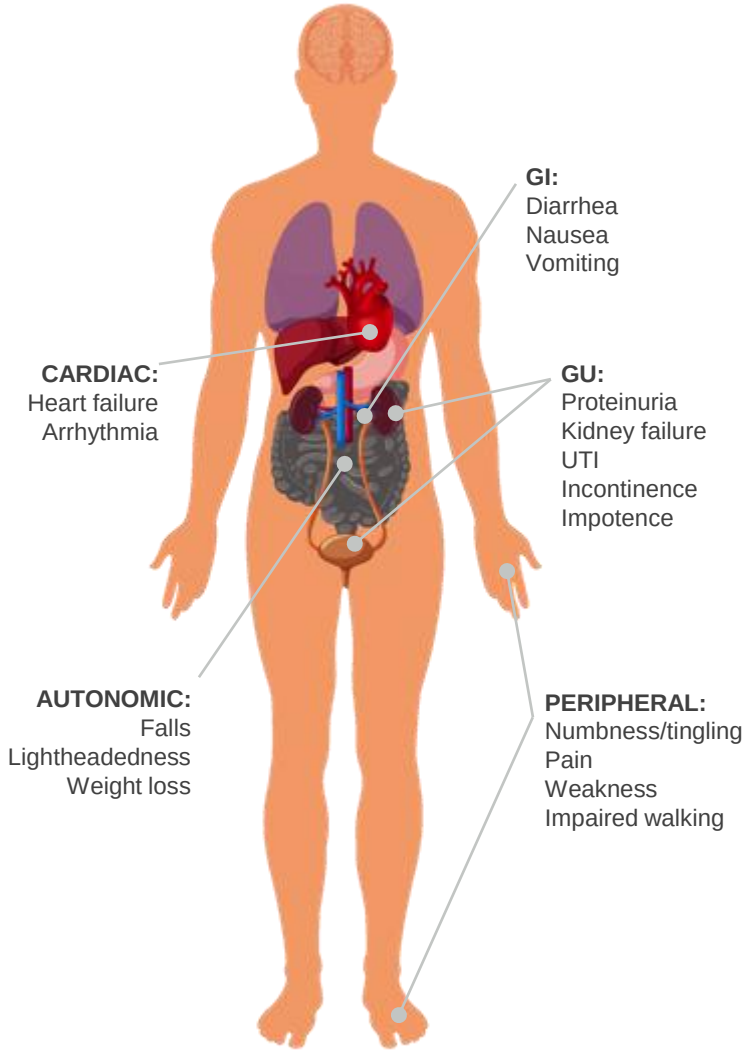
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

patients worldwide

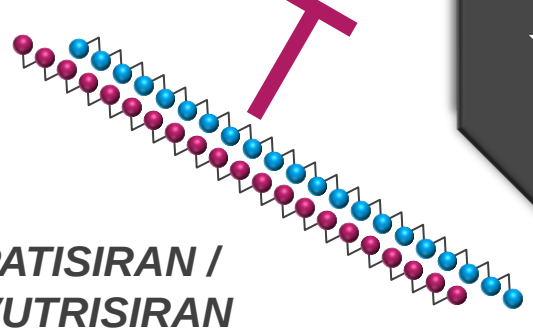


[1] Coelho T, et al. N Engl J Med. 2013;369(9):819-829

* 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 Options, 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

amvuttra (vutrisiran) injection 25 mg/0.5 mL™

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

About AMVUTTRA

- 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;
† AMVUTTRA is approved in the U.S. for the polyneuropathy of hATTR amyloidosis in adults; see Full Prescribing Information †† Vutrisiran 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

Pushkal Garg, M.D.
Chief Medical Officer

AMVUTTRA™ (vutrisiran) Label & Data

Vutrisiran HELIOS·A Phase 3 Study

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

HELIOS·A

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)
- 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

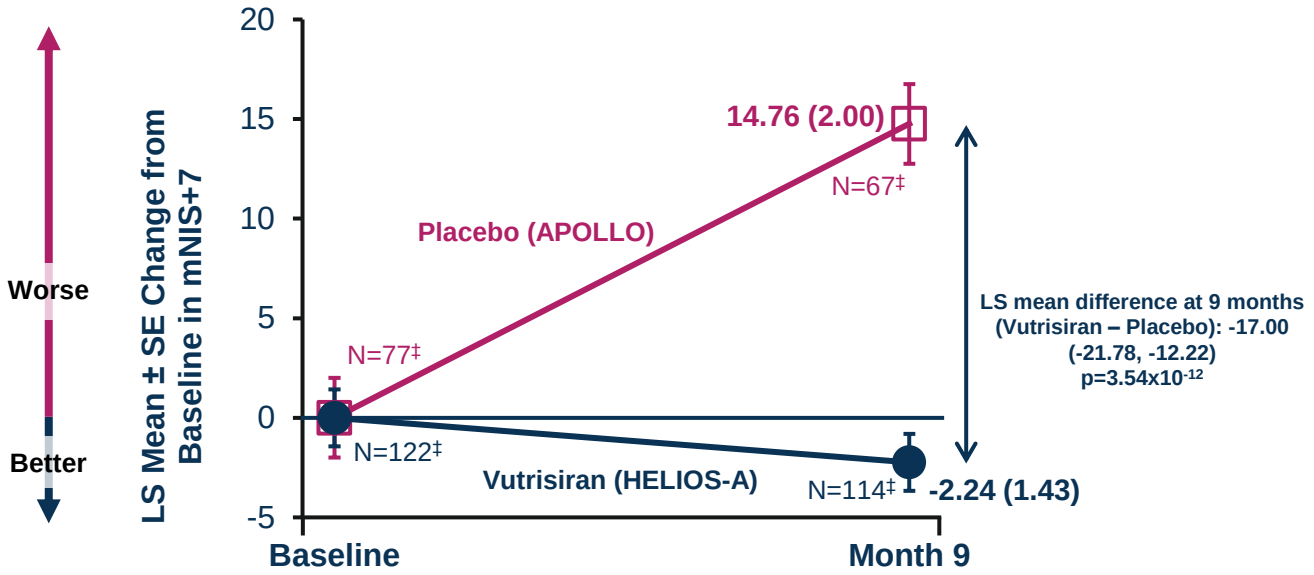
10-MWT, 10-meter walk test; ATTRv, transthyretin-mediated amyloidosis (v for variant); hATTR, hereditary transthyretin-mediated amyloidosis; IV, intravenous; KPS, Karnofsky performance status; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment 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.

HELIOS-A 9-Month Results – Basis of Approval for U.S. Label

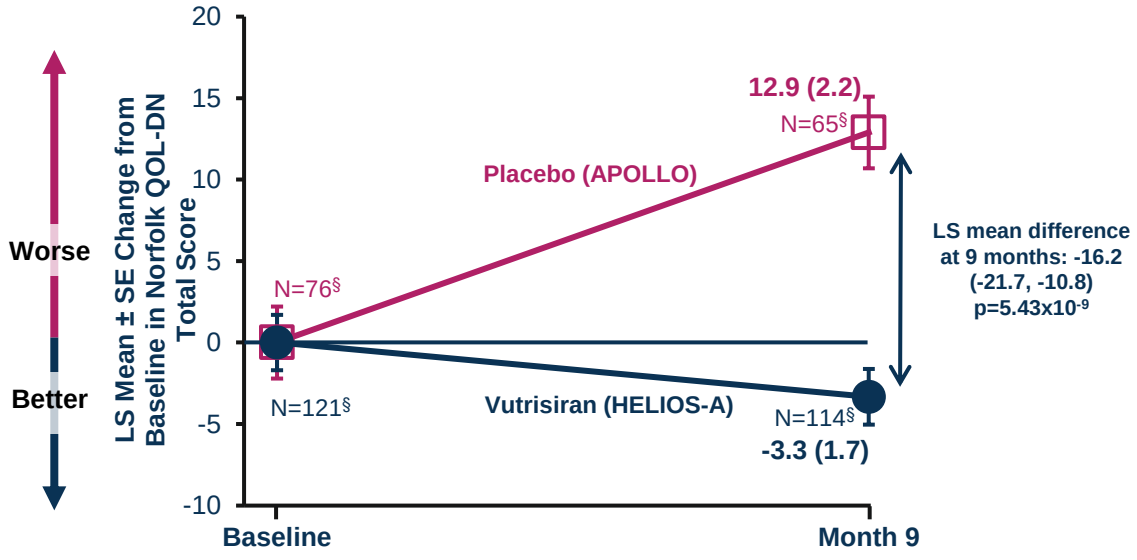
Randomized, Open-Label Study in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy (N=164)

- 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 (50.4% [vutrisiran] vs 18.2% [placebo]) and Norfolk QOL-DN (53.4% vs 23.4%)
- Consistent treatment effects in vutrisiran and patisiran groups in HELIOS-A (data not shown)

mNIS+7 LS Mean Change from Baseline†



Norfolk QOL-DN LS Mean Change from Baseline†



Adams et al., AAN, April 2021 as to primary endpoint and safety/tolerability at Month 9; additional data presented by Alnylam in conference call held April 19, 2021

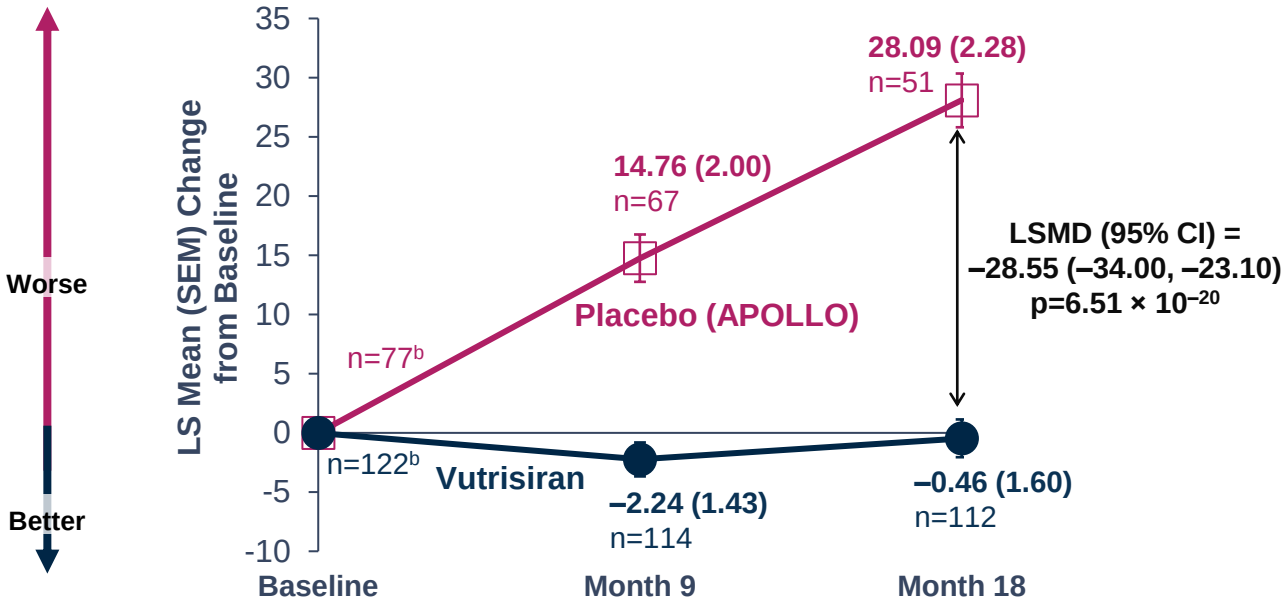
APOLLO refers to the randomized, placebo-controlled Phase 3 study of ONPATTRO (patisiran) in hATTR patients with polyneuropathy (Adams et al, NEJM, 2018). HELIOS-A compares vutrisiran treated hATTR patients with polyneuropathy to the prespecified external placebo group from APOLLO

[a] Improvement defined as patients with <0-point increase from baseline to 18 months.

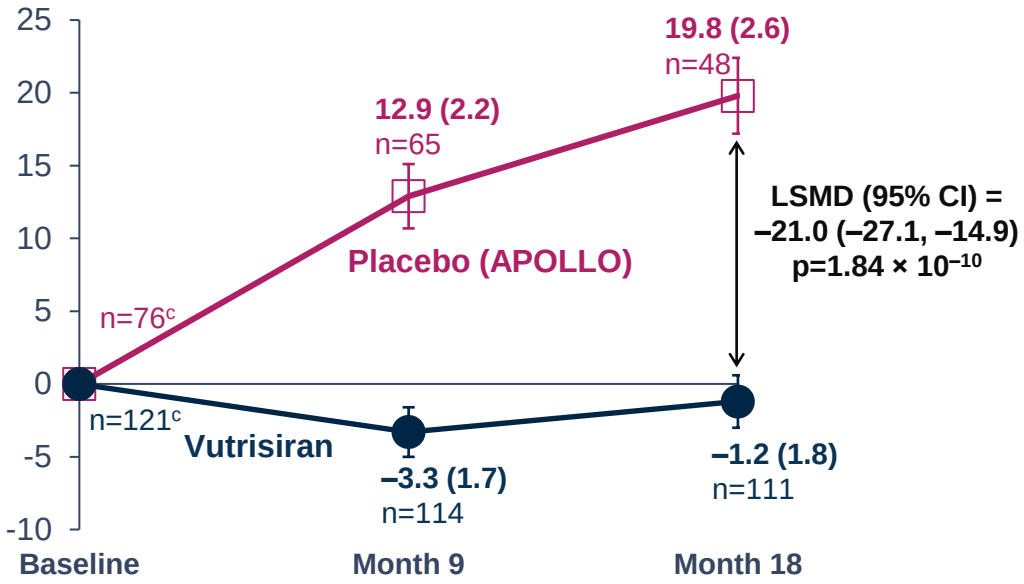
† mITT population. At baseline, the mean (±SD) Norfolk QOL-DN score was 47.1 (26.3) in the vutrisiran group and 55.5 (24.3) in the external placebo group. ‡ mITT population. At baseline, the mean (±SD) 10-MWT was 1.006 (0.393) in the vutrisiran group and 0.790 (0.319) in the external placebo group. § Number of evaluable patients.

HELIOS-A – Results Consistent at 18-Months

mNIS+7 LS Mean Change from Baseline[a]



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



Statistically significant improvements relative to placebo also demonstrated on 10MWT, mBMI and R-ODS

[a] 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. [b] **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.** [c] **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

HELIOS-A Safety Summary – 18 Months

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; 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
- 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 – 18 Months

At least one event, n (%)	APOLLO	HELIOS-A	
	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)

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

AMVUTTRA™ (vutrisiran) U.S. Label

Highlights of Prescribing Information

INDICATIONS AND USAGE

AMVUTTRA is a transthyretin-directed small interfering RNA indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

DOSAGE AND ADMINISTRATION

The recommended dosage of AMVUTTRA is 25 mg administered by subcutaneous injection once every 3 months (quarterly).

AMVUTTRA is for subcutaneous use only and should be administered by a healthcare professional.

DOSAGE FORMS AND STRENGTHS

Injection: 25 mg/0.5 mL in a single-dose prefilled syringe.

WARNINGS AND PRECAUTIONS

Reduced serum vitamin A levels and recommended supplementation: Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.

ADVERSE REACTIONS

The most common adverse reactions (≥5%) were arthralgia, dyspnea, and vitamin A decreased.

These highlights do not include all the information needed to use AMVUTTRA safely and effectively. See full prescribing information for AMVUTTRA.

Vutrisiran HELIOS·B Phase 3 Study

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

N = 655
Patient Population

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

1:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Primary Endpoint

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

Select Secondary Endpoints

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

ClinicalTrials.gov Identifier: NCT04153149

HELIOS·B

Enrollment complete

Topline results on 30-month endpoint expected **early 2024**

Study includes optional interim analysis

Tolga Tanguler

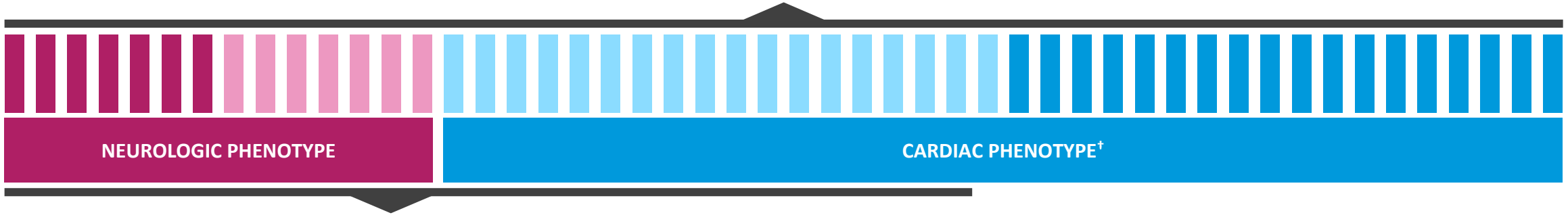
Chief Commercial Officer

Commercialization Strategy

hATTR Amyloidosis Polyneuropathy Market Opportunity

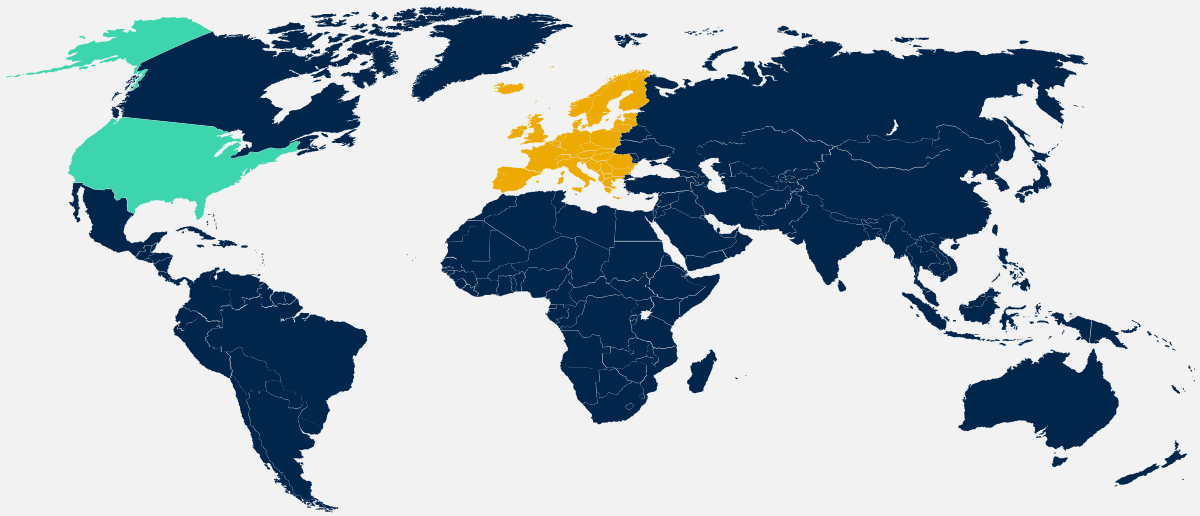
Estimated Disease Prevalence*†

~ 50,000 patients worldwide



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.

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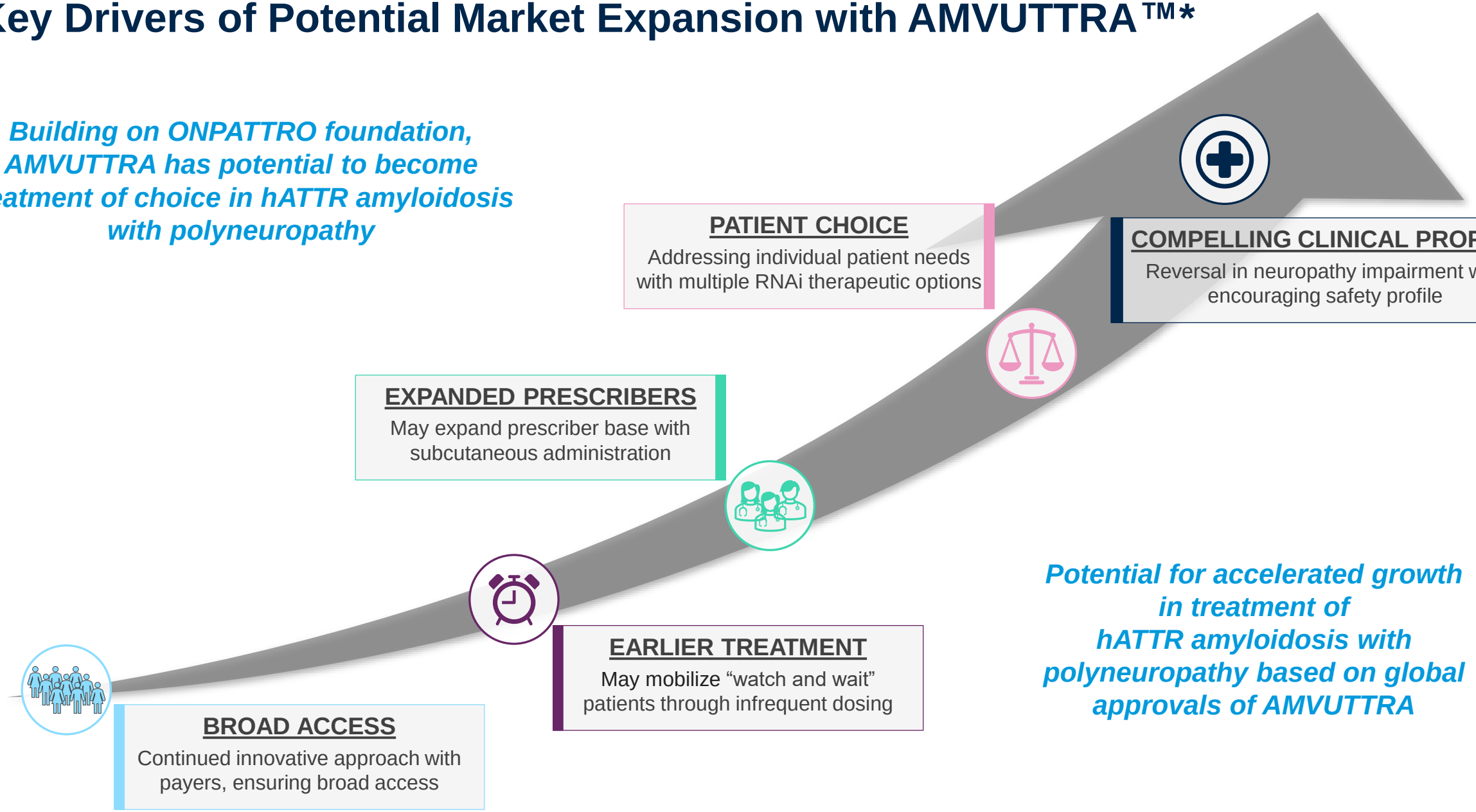
‡ Current diagnosis rates difficult to confirm and may be lower in initial launch years

Key Drivers of Potential Market Expansion with AMVUTTRA™*

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



BROAD ACCESS
Continued innovative approach with payers, ensuring broad access

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

EXPANDED PRESCRIBERS
May expand prescriber base with subcutaneous administration

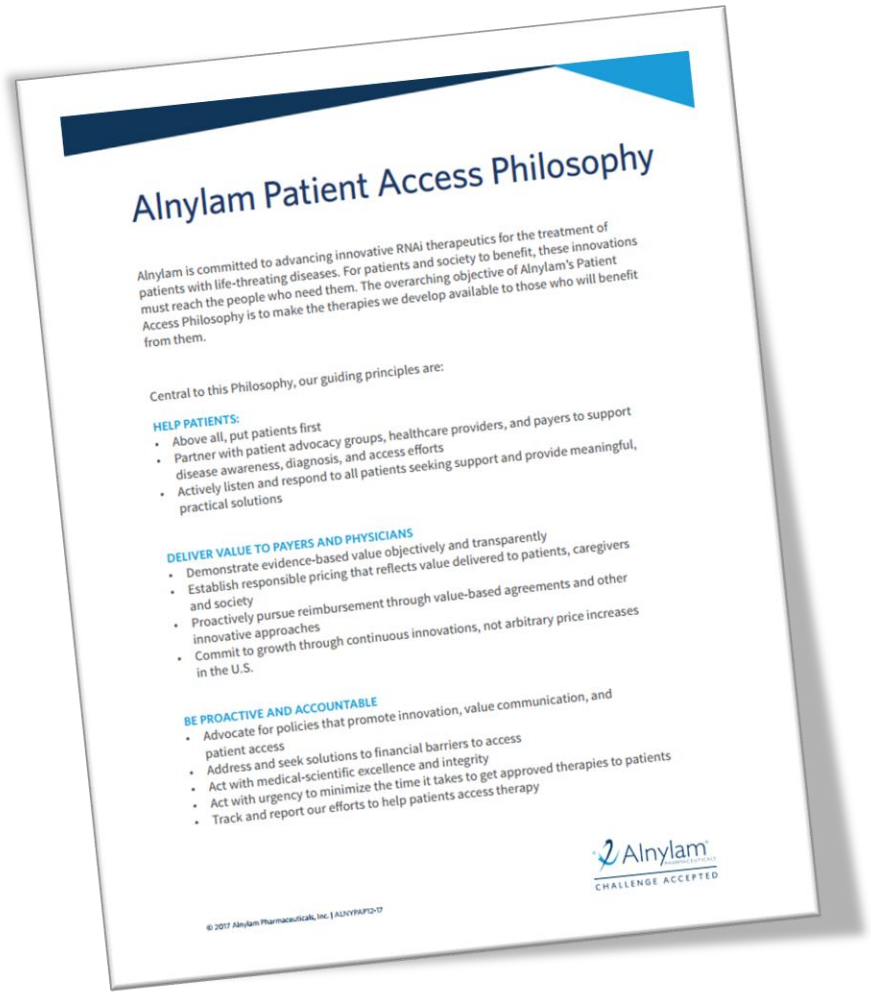
PATIENT CHOICE
Addressing individual patient needs with multiple RNAi therapeutic options

COMPELLING CLINICAL PROFILE
Reversal in neuropathy impairment with encouraging safety profile

Potential for accelerated growth in treatment of hATTR amyloidosis with polyneuropathy based on global approvals of AMVUTTRA

* AMVUTTRA is approved in the U.S. for the PN of hATTR amyloidosis. For additional information on AMVUTTRA, see Full Prescribing Information

Alnylam's Patient Access Philosophy



Alnylam Patient Access Philosophy

Alnylam is committed to advancing innovative RNAi therapeutics for the treatment of patients with life-threating diseases. For patients and society to benefit, these innovations must reach the people who need them. The overarching objective of Alnylam's Patient Access Philosophy is to make the therapies we develop available to those who will benefit from them.

Central to this Philosophy, our guiding principles are:

HELP PATIENTS:
- Above all, put patients first
- Partner with patient advocacy groups, healthcare providers, and payers to support disease awareness, diagnosis, and access efforts
- Actively listen and respond to all patients seeking support and provide meaningful, practical solutions

DELIVER VALUE TO PAYERS AND PHYSICIANS
- Demonstrate evidence-based value objectively and transparently
- Establish responsible pricing that reflects value delivered to patients, caregivers and society
- Proactively pursue reimbursement through value-based agreements and other innovative approaches
- Commit to growth through continuous innovations, not arbitrary price increases in the U.S.

BE PROACTIVE AND ACCOUNTABLE
- Advocate for policies that promote innovation, value communication, and patient access
- Address and seek solutions to financial barriers to access
- Act with medical-scientific excellence and integrity
- Act with urgency to minimize the time it takes to get approved therapies to patients
- Track and report our efforts to help patients access therapy

Alnylam CHALLENGE ACCEPTED

Critical excerpts from Alnylam's Patient Access Philosophy

- Demonstrate evidence-based value objectively and transparently
- Establish responsible pricing that reflects value delivered to patients, caregivers and society
- Proactively pursue reimbursement through value-based agreements and other innovative approaches
- Commit to growth through continuous innovations, not arbitrary price increases in the U.S.

Help Patients | **Deliver Value** | **Be Proactive**

Pricing, Cost & Access Considerations

We evaluated the following five factors when considering the value that AMVUTTRA will provide to patients, their families, insurers, and physicians:

Innovation in ATTR

Represents Alnylam's continuous innovation in ATTR, underscoring Company's commitment to developing TTR Franchise of transformative RNAi therapeutics.

Efficacy Impact

Improved signs and symptoms of polyneuropathy, with >50% of patients experiencing halting or reversal of disease manifestations in HELIOS-A.

Established Safety

Acceptable safety and tolerability profile demonstrated in HELIOS-A.

Infrequent Dosing

Highly differentiated dosing regimen: 25mg subq q3m. HCP-administered with no premedication or laboratory monitoring.

Value Delivered

Alnylam has proven reputation for innovative contracting, including successful value-based contracts based on established VBA frameworks.

Annual List Price: $463,500

Making AMVUTTRA™ Available

Commercial Excellence, Diagnosis and Education, Patient Support, and Access are Key Priorities

COMMERCIAL FIELD TEAM

Account Management

Marketing

Patient Support Services

Coverage & Reimbursement

Market Access

DISEASE EDUCATION

Medical Affairs

Advocacy Support

the BRIDGE hATTR amyloidosis

HEREDITARY ATTR AMYLOIDOSIS

SUPPORT SERVICES

Alnylam ASSIST™

Personalized support services, including access to in-house Case Managers and field-based Patient Education Liaisons.

Includes financial support for eligible patients.

PATIENT ACCESS

Value-Based Agreements tied to clinical experience

Price increase protection

AMVUTTRA™ (vutrisiran) FDA Approval

Q&A Session