Positive Topline Results from HELIOS-B Phase 3 Study of Vutrisiran

June 24, 2024

Agenda

Welcome

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

Introduction

- **Yvonne Greenstreet, MBChB, MBA**
  Chief Executive Officer

HELIOS-B Topline Results

- **Pushkal Garg, M.D.**
  Chief Medical Officer

Commercialization Strategy

- **Tolga Tanguler**
  Chief Commercial Officer

Q&A Session

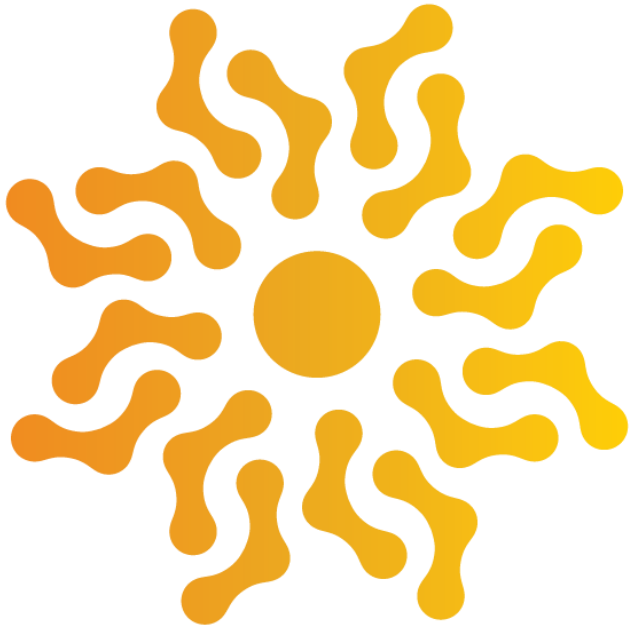
Alnylam Forward Looking Statements

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. All statements other than historical statements of fact regarding Alnylam's expectations, beliefs, goals, plans or prospects including, without limitation, Alnylam's estimations regarding the size of the potential patient population and the number of patients who are dissatisfied with their current treatment regimens; Alnylam's expectations regarding the safety and efficacy of vutrisiran for the treatment of ATTR amyloidosis with cardiomyopathy, including its potential to be standard of care in ATTR-CM; the potential for vutrisiran to halt disease progression that patients experience with ATTR-CM, including across key measures of disease burden; the potential for vutrisiran to obtain regulatory approval for the treatment of ATTR amyloidosis with cardiomyopathy; Alnylam's belief that vutrisiran is well positioned to address unmet medical need as the first and only RNAi therapeutic for both polyneuropathy and cardiomyopathy manifestations of ATTR amyloidosis; the expected timing of the presentation of full data from the HELIOS-B clinical trial and the filing of a U.S. Supplemental New Drug Application for vutrisiran; Alnylam's plans to use a Priority Review Voucher in connection with the Supplemental New Drug Application for vutrisiran; the potential for vutrisiran's clinical profile to support first-line positioning in newly diagnosed patients and in those patients who continue to experience disease progression with stabilizers; the potential for vutrisiran to have a market-leading profile in ATTR-CM; and the potential for vutrisiran to unlock future growth and value creation should be considered forward-looking statements.

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, risks and uncertainties relating to: Alnylam's ability to successfully execute on its *"Alnylam P^{5}x25 "* strategy; Alnylam's ability to successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for Alnylam's product candidates, including vutrisiran; actions or advice of regulatory agencies and Alnylam's ability to obtain regulatory approval for its product candidates, including vutrisiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling Alnylam's approved products globally; and any delays, interruptions or failures in the manufacture and supply of Alnylam's product candidates or its marketed products; as well as those risks more fully discussed in the "Risk Factors" filed with Alnylam's 2023 Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC), as may be updated from time to time by Alnylam's subsequent Quarterly Reports on Form 10-Q and in its other SEC filings. In addition, any forward-looking statements represent Alnylam's views only as of today and should not be relied upon as representing its views as of any subsequent date. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

Yvonne Greenstreet, MBChB, MBA
Chief Executive Officer

Introduction



HELIOS-B

POSITIVE TOPLINE RESULTS

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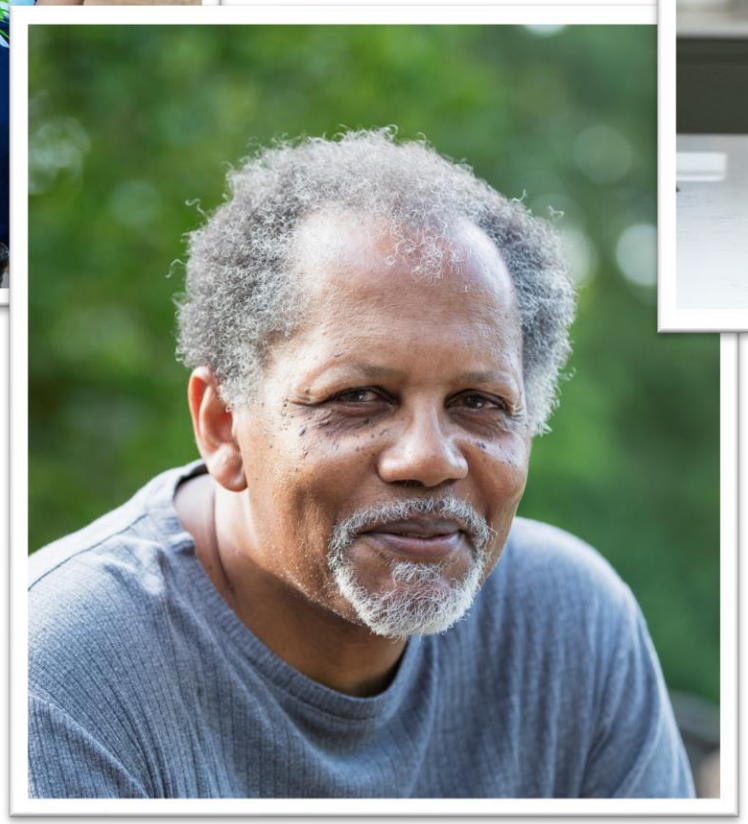
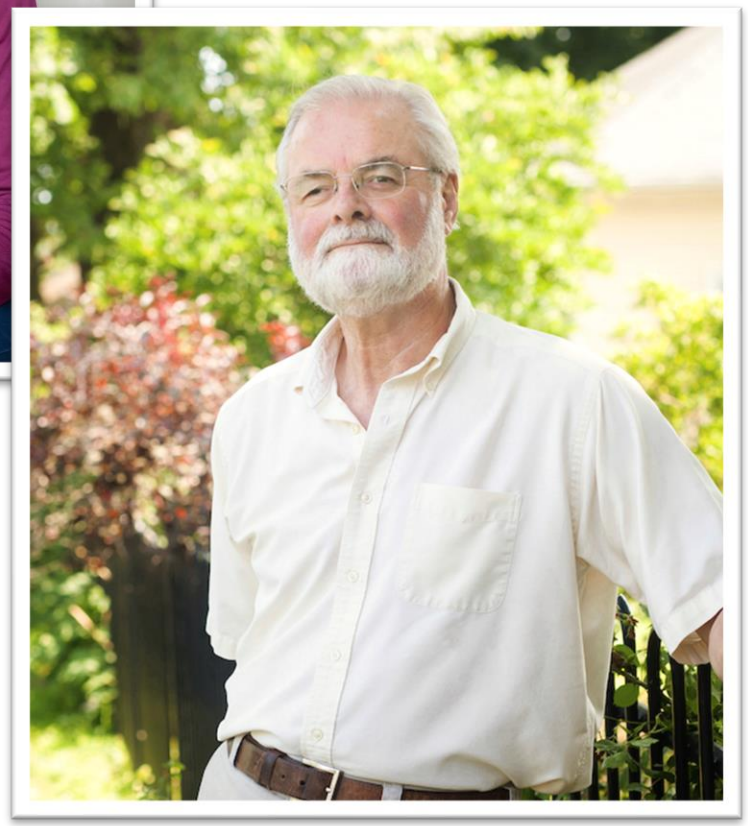




Pushkal Garg, M.D.
Chief Medical Officer

HELIOS-B Topline Results

ATTR Amyloidosis

Rare, Progressively Debilitating, and Fatal Disease

Description

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

Hereditary ATTR (hATTR) Amyloidosis

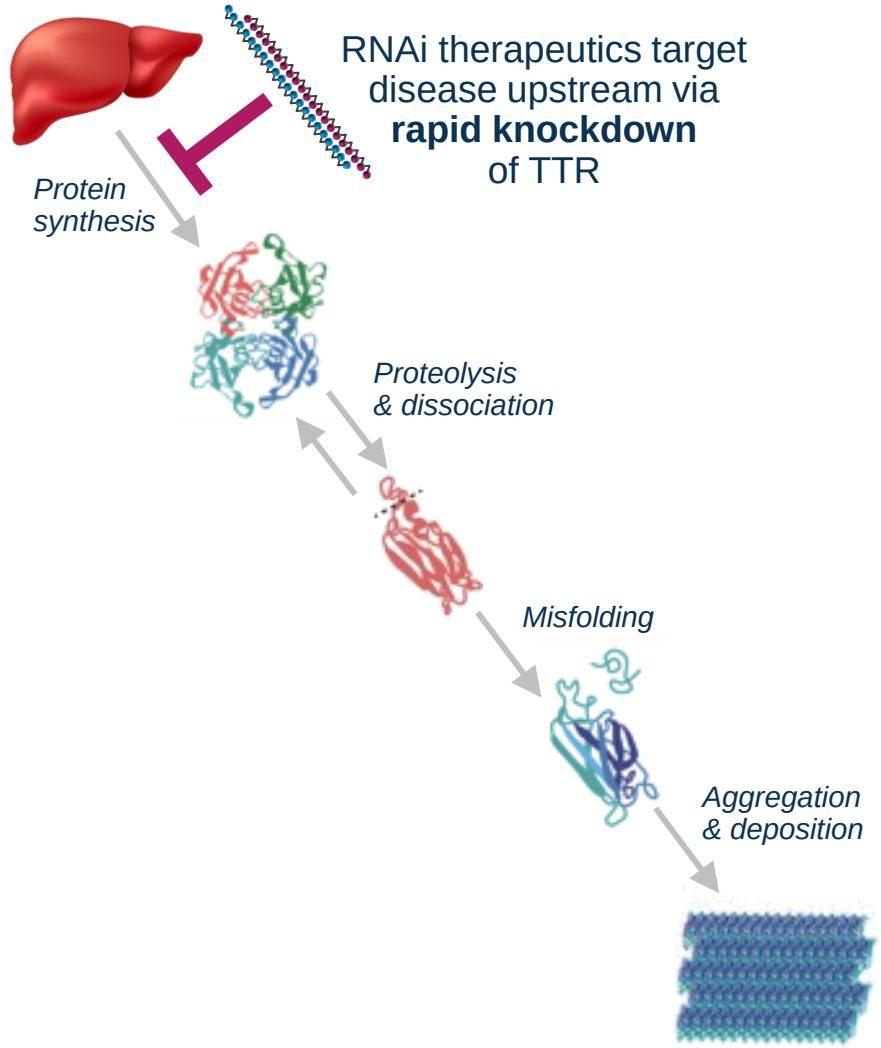
~50,000

patients worldwide[2]

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000–300,000

patients worldwide[3]



1. Coelho T, et al. *N Engl J Med*. 2013;369(9):819-829
2. Ando, et al. *Orphanet J Rare Dis*, 2013; Ruberg, et al. *Circulation*, 2012 (includes hATTR amyloidosis patients with polyneuropathy and cardiomyopathy); Gertz, et al. *Am J Manag Care*. 2017;23:S107-S112
3. Information based on Alnylam modeling data

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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
- 40% of patients on tafamidis 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 up to 36 months, in:
  - Overall population
  - Monotherapy population

Secondary Endpoints

- 6-MWT distance (change from baseline at month 30)
- KCCQ score (change from baseline at month 30)
- All-cause mortality (up to month 42)
- NYHA Class (percent stable or improved at month 30)

Positive topline results reported **June 2024**

sNDA submission using Priority Review Voucher expected **late 2024**

HELIOS·B

ClinicalTrials.gov Identifier: NCT04153149

* Randomization stratified by: 1) baseline tafamidis use (yes versus no); 2) ATTR disease type (hATTR versus wtATTR amyloidosis with cardiomyopathy); and 3) NYHA Class I or II and age <75 years versus all other.

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Prespecified Primary and Secondary Endpoint Structure

	Overall population (N=654)	Monotherapy population (N=395)
PRIMARY ENDPOINT		
Composite outcome of all-cause mortality and recurrent CV events up to 36 months		
SECONDARY ENDPOINT		
6-minute walk test (6-MWT) (change from baseline at 30 months)		
Kansas City Cardiomyopathy Questionnaire (KCCQ) (change from baseline at 30 months)		
All-cause mortality (up to 42 months)		
New York Heart Association (NYHA) Class (% stable or improved at 30 months)		

Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of ATTR amyloidosis with cardiomyopathy have not been established or evaluated by the FDA, EMA or any other health authority.

Achieved Primary and All Secondary Endpoints in Both Overall and Monotherapy Populations

	Overall population (N=654)	Monotherapy population (N=395)
PRIMARY ENDPOINT		
Composite outcome of all-cause mortality and recurrent CV events up to 36 months	HR=0.718 p=0.0118	HR=0.672 p=0.0162
SECONDARY ENDPOINT		
6-minute walk test (6-MWT) (change from baseline at 30 months)	p<0.025	p<0.025
Kansas City Cardiomyopathy Questionnaire (KCCQ) (change from baseline at 30 months)	p<0.025	p<0.025
All-cause mortality (up to 42 months)	HR=0.645 p<0.025	HR=0.655 p<0.05
New York Heart Association (NYHA) Class (% stable or improved at 30 months)	p<0.025	p<0.025

Consistent effects on primary composite endpoint and all secondary endpoints observed across all key subgroups, including baseline tafamidis use, ATTR disease type, and measures of disease severity

Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of ATTR amyloidosis with cardiomyopathy have not been established or evaluated by the FDA, EMA or any other health authority.

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Encouraging Safety and Tolerability

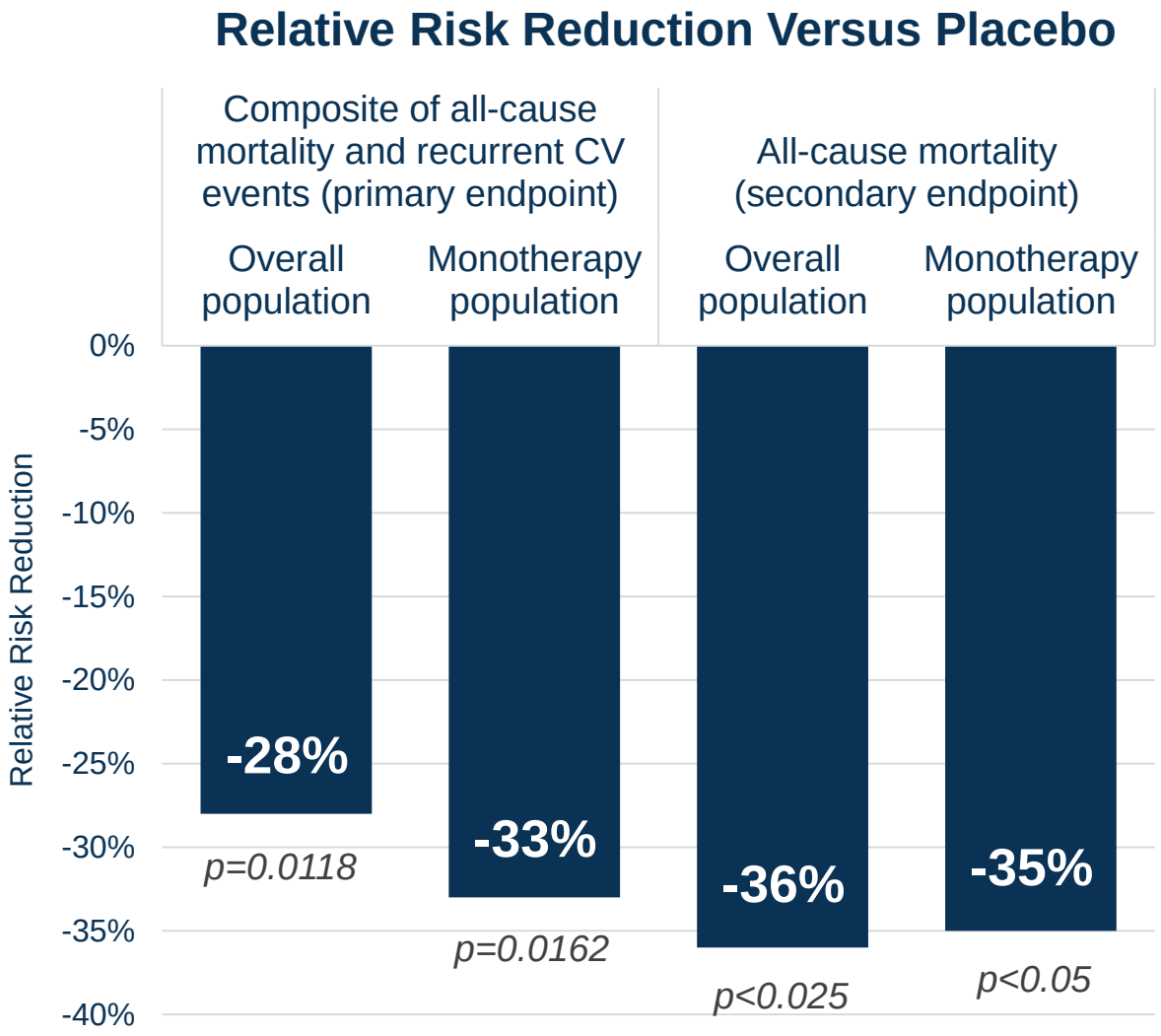
Consistent With Established Profile

Safety	Vutrisiran (N=326)	Placebo (N=328)
Adverse Events (AEs)	98.8%	98.5%
Serious Adverse Events	61.7%	67.1%
AEs leading to study drug discontinuation	3.1%	4.0%

No AEs were seen ≥3% more frequently with vutrisiran compared with placebo.

Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of ATTR amyloidosis with cardiomyopathy have not been established or evaluated by the FDA, EMA or any other health authority.

Data Support Potential for Vutrisiran to Become Standard of Care in ATTR-CM



- Clinically significant benefits on 6MWT, KCCQ, and NYHA class – key measures of disease progression
- Consistent effects observed in all key subgroups, including baseline tafamidis
- Encouraging safety and tolerability, consistent with established profile

Primary composite endpoint of all-cause mortality and recurrent CV events included data up to 36 months; Secondary endpoint of all-cause mortality included data up to 42 months.

Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of ATTR amyloidosis with cardiomyopathy have not been established or evaluated by the FDA, EMA or any other health authority.

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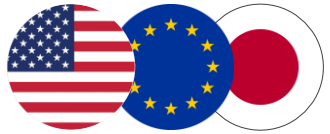
Next Steps

HELIOS-B Full Results

Submitted as a Late-Breaking Abstract to ESC Congress
(Aug 30 – Sept 2, London)



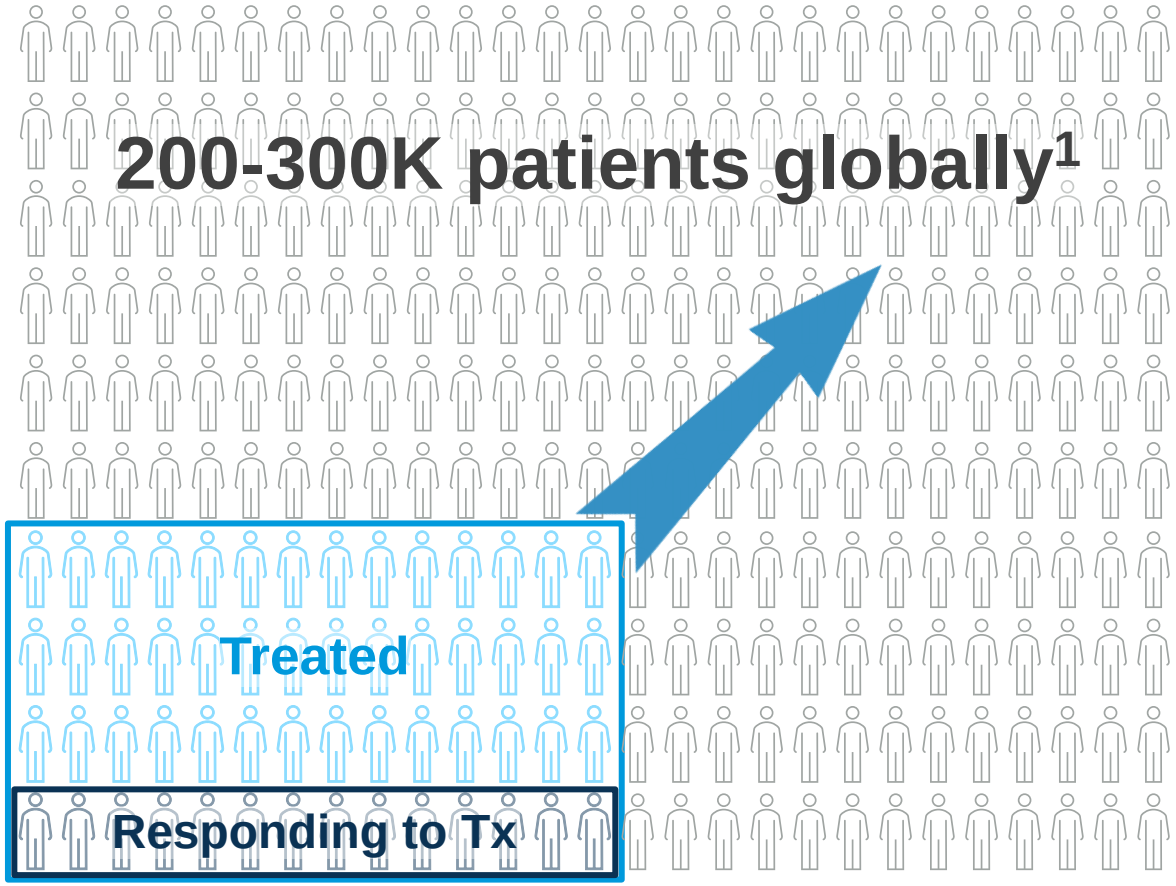
Global Regulatory Submissions – Late 2024

Priority Review Voucher to Accelerate FDA Review

Tolga Tanguler
Chief Commercial Officer

Commercialization Strategy

Significant Unmet Need Remains Among ATTR-CM Patients



~80%

ATTR-CM patients untreated globally[1]

- Diagnostic rates rapidly improving
- Analogues suggest competition accelerates category growth

~75%

Patients have partial or no response to current treatment, per HCPs[2]

- HCPs prioritize impact on mortality, CV events and functional capacity[3]
- Looking for better symptomatic and QoL impact, and greater impact on disease progression[3]

1. ATTR-CM, based on Alnylam modeling data, 2. Alnylam market research with HCPs (n=530), 3. Alnylam Market Research with HCPs (n = 100)

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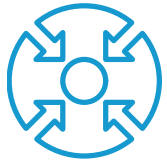
Vutrisiran Well Positioned for Market-Leading Profile in ATTR-CM

Features Physicians Consistently Look for in a First-Line Therapy[1]

- ✓ Efficacy
  - Clinical Outcomes
  - Symptomology, QoL, Function
- ✓ Safety/Tolerability
- ✓ Ease of Use
- ✓ Access

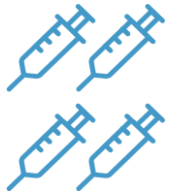


Unique MOA

- **Targeted RNAi mechanism** enables **rapid knockdown** of pathogenic protein at the source
- Works **upstream of approved medicine**

Data Support Potential First-Line Use

- Significant reduction in **mortality** and **CV hospitalizations**
- Substantial impact on **measures of disease progression**
- **Consistent effects** across all key trial subgroups
- **Encouraging safety,** consistent with established profile



Only 4 Doses per Year

- **Quarterly, subcutaneous dosing,** supporting strong adherence, aligning with MD visits
- **Site of care flexibility**

Favorable Payer Dynamics

- **Part B** coverage expected to result in majority of patients having **$0 out-of-pocket costs**
- Monotherapy favored by payers prior to tafamidis LOE

1. Alnylam market research with HCPs (n=530)

Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of ATTR amyloidosis with cardiomyopathy have not been established or evaluated by the FDA, EMA or any other health authority.

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Alnylam Poised for Market Leadership in ATTR Amyloidosis

Demonstrated Impact & Leadership in hATTR-PN

Driving Category Growth

>50% growth in prescribers YoY

Market Leading Tx Choice

~90% Alnylam market share in hATTR-PN

Enabling Patient Access

>99% of patients have confirmed access

~70% of patients have no out-of-pocket costs

Strong Adherence & Compliance

>95% of patients comply with AMVUTTRA dosing regimen and remain on therapy

Poised to Maximize Significant Opportunity in ATTR-CM

Deep experience with TTR Centers

Well positioned to serve unmet needs of ATTR-CM patients

Focused Customer-Facing Teams

Delivering seamless customer experiences, differentiating in competitive landscape

Strong Payer and Health Systems Partnerships

Exceptional patient access through excellence in account management and clinical education

Established Patient Support Services

Optimized time to therapy, strong compliance

Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of ATTR amyloidosis with cardiomyopathy have not been established or evaluated by the FDA, EMA or any other health authority.
hATTR: hereditary transthyretin-mediated; PN: polyneuropathy; Internal data and market data estimation; Individual patient coverage varies based on insurance plan

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HELIOS-B Catalyzes Future Growth and Value Creation for Alnylam

Potential for Standard of Care

Well Positioned to Address Significant Unmet Need in ATTR-CM

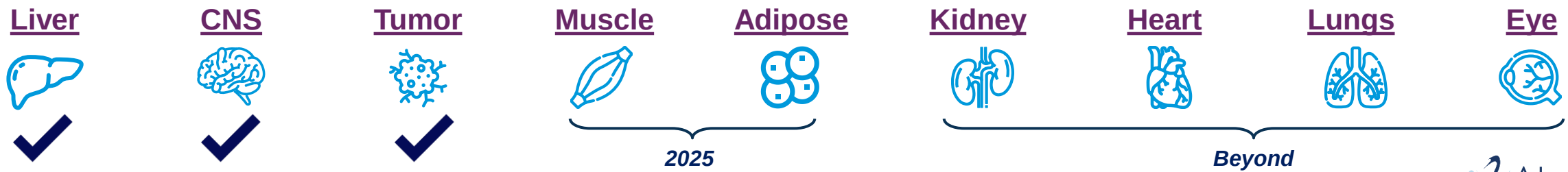
Anchor Commercial Franchise

HELIOS-B Catalyzes Future Growth and Value Creation for Alnylam

	IND-ENABLING	PHASE 1	PHASE 2	PHASE 3	APPROVED
ONPATTRO® (patisiran)	hATTR Amyloidosis with Polyneuropathy				
AMVUTTRA® (vutrisiran)	hATTR Amyloidosis with Polyneuropathy				
GIVLAARI® (givosiran)	Acute Hepatic Porphyria				
OXLUMO® (lumasiran)	Primary Hyperoxaluria Type 1				
LEQVIO® (inclisiran)					
Vutrisiran			ATTR Amyloidosis with Cardiomyopathy		
Fitusiran					
Cemdisiran					
Cemdisiran			Paroxysmal Nocturnal Hemoglobinuria		
Zilebesiran					
Mivelsiran					
Elebsiran			Hepatitis B Virus Infection		
Elebsiran					
ALN-HSD			NASH		
ALN-TTRsc04					
Mivelsiran			Alzheimer's Disease		
ALN-SOD1			ALS		
ALN-PNP					
ALN-KHK			Type 2 Diabetes Mellitus		
ALN-BCAT					
ALN-HTT02	Huntington's Disease				
ALN-Gene A	Bleeding Disorders				
ALN-Gene Y	Type 2 Diabetes Mellitus				

Vutrisiran's approval in ATTR-CM would:

- ✓ Secure next wave of significant topline growth
- ✓ Enable significant reinvestment in productive organic R&D platform
- ✓ Accelerate transition into leading global biotech



Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of ATTR amyloidosis with cardiomyopathy have not been established or evaluated by the FDA, EMA or any other health authority.
Table does not reflect partnered programs or programs with economic commitments to third parties.

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HELIOS-B Phase 3 Topline Results

Q&A Session

Thank You!

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