Building a Top-Tier Biotech

43rd Annual J.P. Morgan Healthcare Conference

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Chief Executive Officer

January 13, 2025

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, statements regarding Alnylam's aspiration to become a top-tier biotech company and the planned achievement of its "*Alnylam P^{5}x25*" goals; the potential for Alnylam to identify new potential drug development candidates and advance its research and development programs, including statements regarding the number of CTAs that Alnylam expects to file in coming years, the number of clinical programs that Alnylam expects to pursue by the end of 2025, and the potential benefits of Alnylam's product candidates; Alnylam's ability to obtain approval for new commercial products or additional indications for its existing products, including AMVUTTRA; the size of the commercial opportunities for Alnylam's current and any future products and the number of patients that could be treated by such products, including AMVUTTRA; the potential expansion of Alnylam's TTR franchise; Alnylam's expectations regarding the safety and efficacy of AMVUTTRA for the treatment of ATTR-CM and the potential for AMVUTTRA to become a first line treatment for ATTR-CM; Alnylam's expectations that AMVUTTRA will have favorable pricing and reimbursement dynamics; and Alnylam's projected commercial and financial performance, including the expected range of net product revenues for 2025 and Alnylam's expectation that achievement of its 2025 net product revenue guidance positions it to achieve non-GAAP profitability, 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*" goals; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for Alnylam's product candidates; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, as well as favorable pricing and reimbursement; successfully launching, marketing and selling Alnylam's approved products globally; delays, interruptions or failures in the manufacture and supply of Alnylam's product candidates or its marketed products; obtaining, maintaining and protecting intellectual property; Alnylam's ability to successfully expand the approved indications for AMVUTTRA; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations and its ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; Alnylam's ability to maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products, including Roche, Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with Alnylam's most recent periodic report (Quarterly Report on Form 10-Q or Annual Report on Form 10-K) filed with the SEC and in its other SEC filings. In addition, any forward-looking statements represent Alnylam's views only as of the date of this presentation and should not be relied upon as representing Alnylam's views as of any subsequent date. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

The Leader in RNAi Therapeutics

Outstanding R&D Productivity

- **Proven platform** that has pioneered new class of medicines
- **5** approved medicines

Rich Pipeline with Multiple Blockbuster Opportunities

- **>25 high-value programs** expected in clinic across diverse indications by end of 2025

Leading Commercial Capabilities Driving Strong Performance

- Significant share and consistent growth, including in competitive markets
- **33% YoY** growth in net product revenue

On Track to Deliver on *Alnylam P^{5}x25* Financial Goals

- **≥40% revenue CAGR** expected through YE 2025*
- **Sustainable non-GAAP profitability** expected in 2025

** Since time of inception of "Alnylam P^{5}x25" goals at YE 2020*

Alnylam

2024 Delivered Strong Progress Across the Business

Portfolio & Pipeline

HELIOS-B

Highly Positive HELIOS-B Phase 3 results

PRIORITY

Global regulatory filings for **vutrisiran,** PDUFA date March 23, 2025

Positive **nucresiran** (ALN-TTRsc04) Phase 1 data supporting potential for best-in-class profile

Positive initial multi-dose results with **mivelsiran**

Initiated cAPPricorn-1 Phase 2 study in CAA

KARDIA

Positive **zilebesiran** Phase 2 results showing significant additive blood pressure lowering

Expanded clinical pipeline with **4 proprietary CTAs:**

- ALN-HTT02
- ALN-AGT-REVERSIR
- ALN-6400
- ALN-4324

Financials & Culture

onpattro (patisiran)

amvuttra (vutrisiran)

GIVLAARI (givosiran)

OXLUMO (lumasiran)

Combined net product revenues: **$1,646 million* (33% growth YoY)**

Maintained strong financial position **$2.7 billion in cash** at year-end 2024*

The Boston Globe TOP PLACES TO WORK 2015-2024

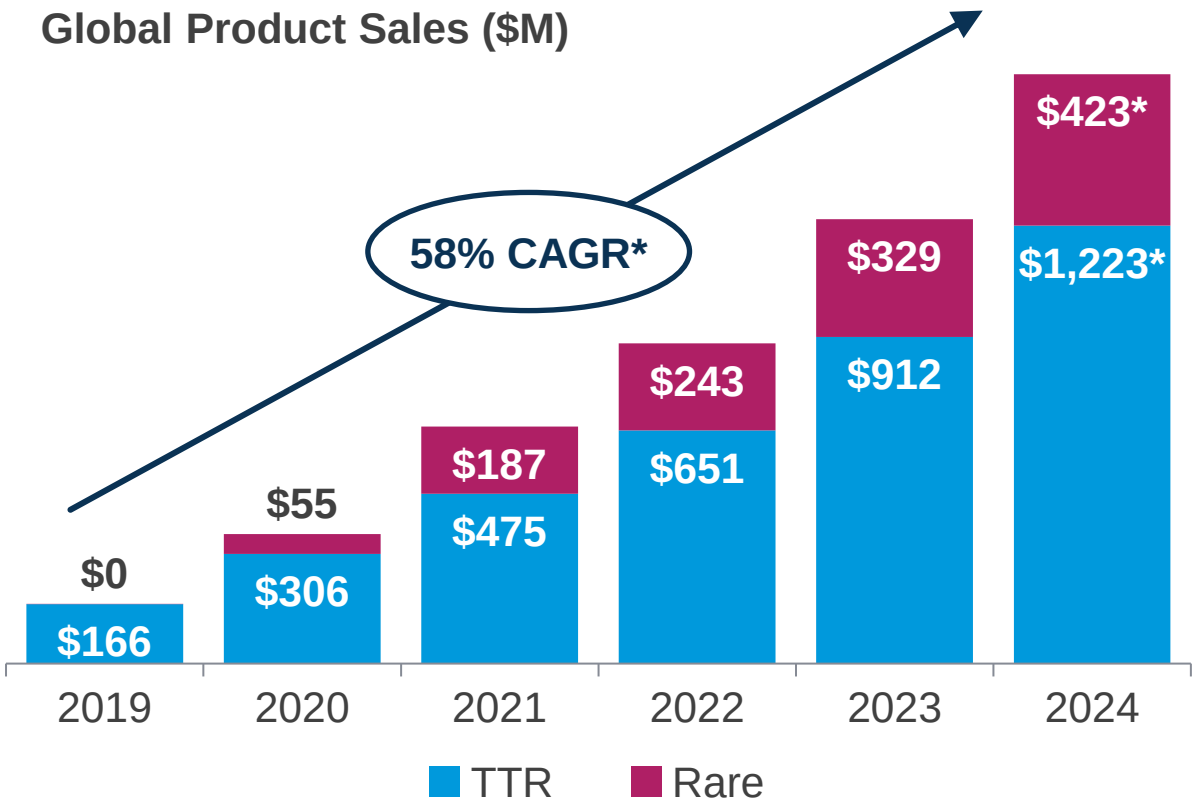
Continued recognition of **award-winning culture**

** Preliminary selected financial results are unaudited, subject to adjustment, and provided as an approximation in advance of the Company's announcement of complete financial results in February 2025.*

Strong Commercial Performance, Exceptional Growth Potential

Transformational Medicines Delivering $1,646 Million in Annual Product Revenues in 2024*

Robust 33% 2024 YoY Growth* in Total Net Product Revenues



Total TTR

onpattro® (patisiran) amvuttra® (vutrisiran)

34%*

YoY growth in Total TTR revenues

Total Rare

GIVLAARI® (givosiran) OXLUMO® (lumasiran)

29%*

YoY growth in Total Rare revenues

** Preliminary selected financial results are unaudited, subject to adjustment, and provided as an approximation in advance of the Company's announcement of complete financial results in February 2025.*

Alnylam®

2025: A Landmark Year for Alnylam

Best-in-Class Team + Award-Winning Culture

Alnylam

TTR Leadership

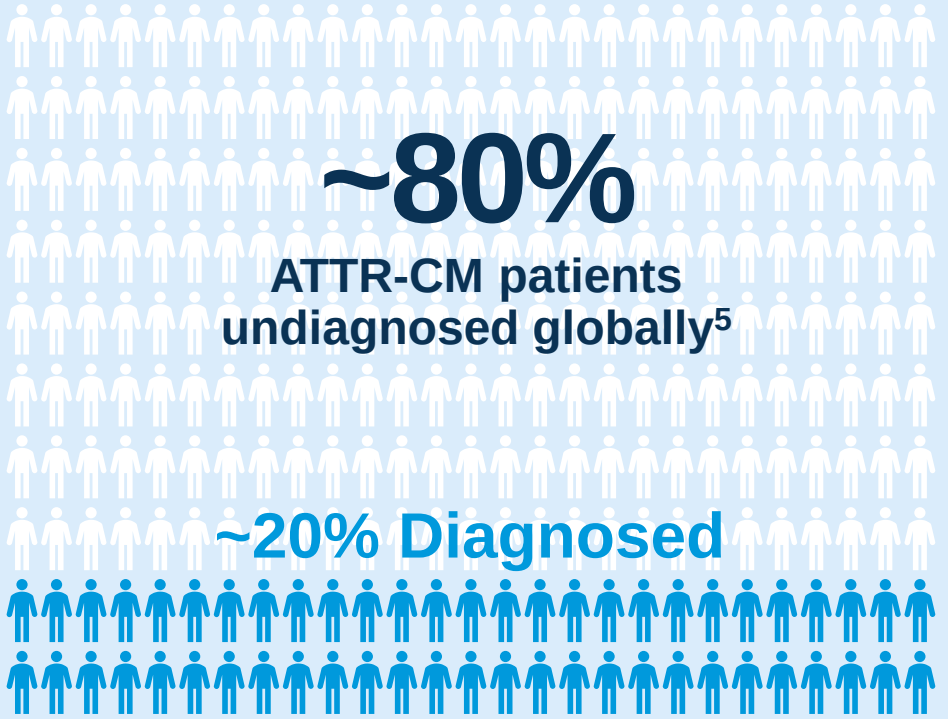
Substantial Opportunity in ATTR Amyloidosis

Rapidly Progressive, Debilitating & Fatal

- Caused by **misfolded transthyretin (TTR)** protein that accumulates as amyloid deposits in multiple tissues including heart, nerves, GI tract[1]
- Deposition of **toxic misfolded TTR** causes irreversible damage and premature death[2,3]
- **Rapid knockdown** of TTR addresses the underlying cause of ATTR amyloidosis[2-4]

Significant Unmet Patient Need

>300K patients globally[5]



References: 1. Coelho T, et al. N Engl J Med. 2013;369(9):819-829. 2. Dasari AKR, et al. *Biochemistry.* 2022;61(21):2358-2365. *3.* Ghosh S, et al. *Amyloid.* 2023;30(4):379-393. *4.* Adams D, et al. *Amyloid.* 2023;30(1):18-26. 5. *Information based on Alnylam modeling data*

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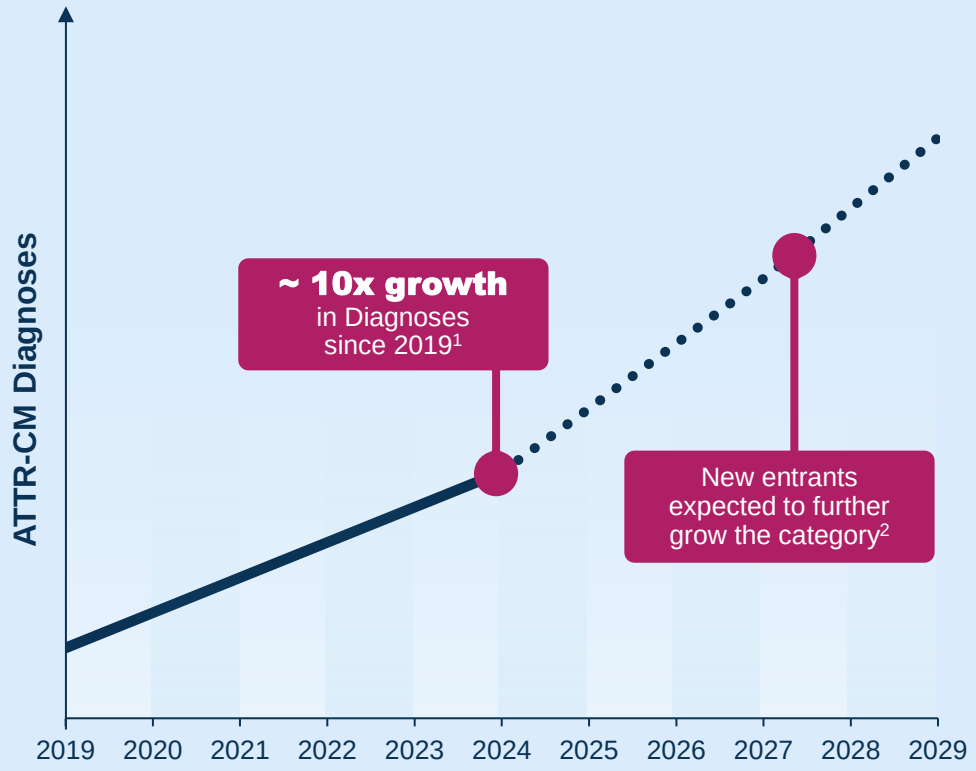
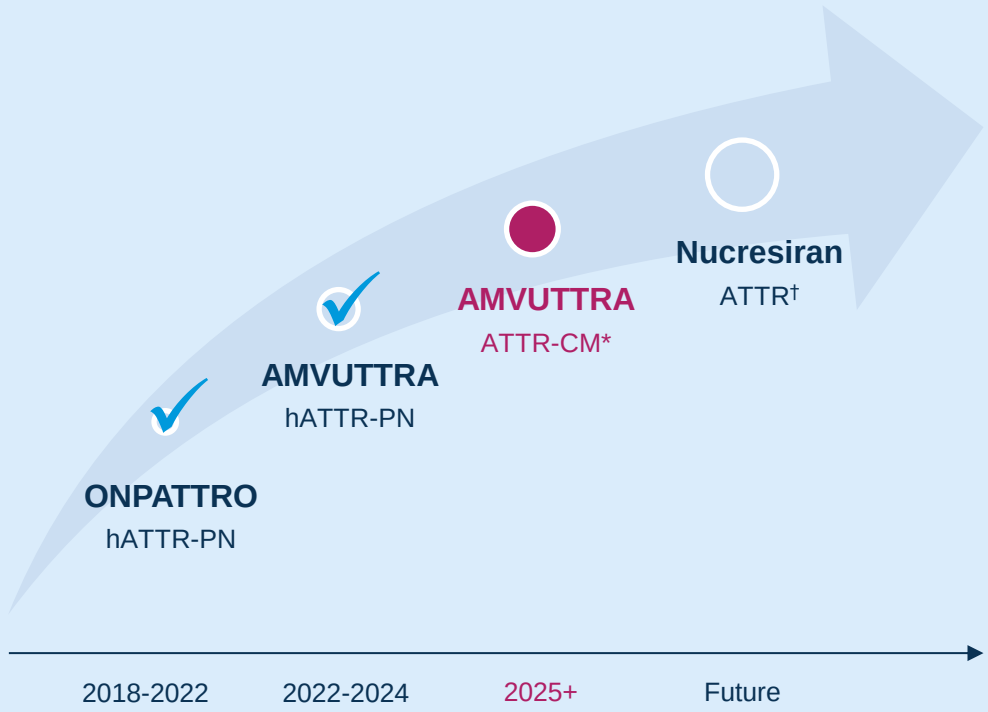
Alnylam ATTR Franchise Poised for Durable Growth

Growing Category, Rapidly Improving Dx



1. Alnylam internal market research, U.S. specific diagnosis rate given data availability.
2. Analog Assessment.

Built for Unmatched Leadership & Longevity



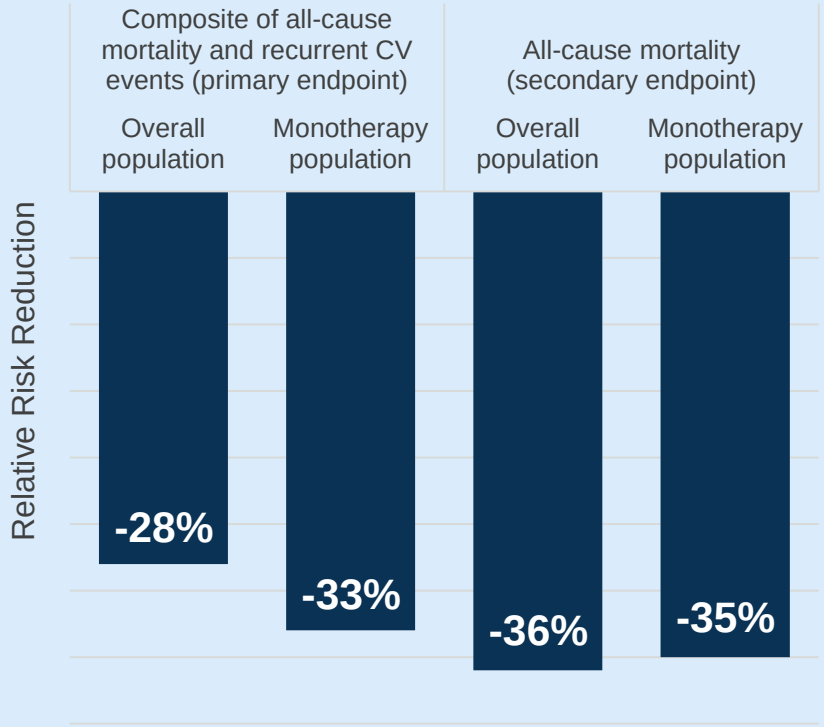
* Pending regulatory approval

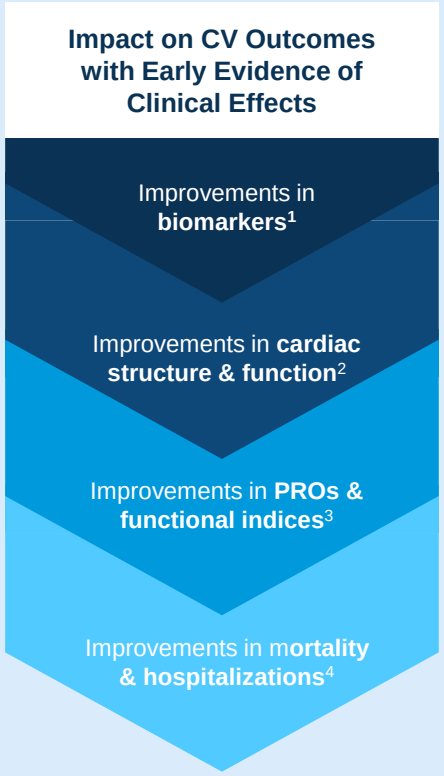
† In development, safety & effectiveness have not yet been established

Number and rate of ATTR-CM diagnoses is provided for illustrative purposes only and does not reflect an exact depiction of the number of patients diagnosed in any year.

Vutrisiran Therapeutic Profile Supports First-Line Potential

HELIOS-B Study Demonstrated Impact of Rapid Knockdown in Population Representative of Today's ATTR-CM Patients





4 doses per year

~95% adherence

as demonstrated in hATTR-PN†

HELIOS-B study, M.Fontana et al, NEJM September 2024; 1. 32% RRR for both NT-proBNP and Tropinin I at Month 30; 2. Improvement vs placebo in LV wall thickness, LV ejection fraction, and parameters of diastolic function at month 30; 3. At 30 months, 6-minute walk test: least-squares (LS) mean difference, 26.5 m; 95% CI, 13.4 to 39.6; P<0.001); KCCQ-OS score: LS mean difference, 5.8 points; 95% CI, 2.4 to 9.2; P<0.001); improvement or no change in NYHA class (LS mean difference, 8.7 percentage points; 95% CI, 1.3 to 16.1; P=0.02); 4. 28% reduction in time to first CV event or all-cause mortality in overall population, 36% reduction in pre-specified secondary endpoint of all-cause mortality in overall population; † Internal data; 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.

Focused Strategy for AMVUTTRA Growth

Launch Priority

New to Treatment

GLOBAL EST. SIZE[1]

~18K Annually

GOAL

Establish AMVUTTRA as first-line choice

Stabilizer Progressors[2]

~20K

Capture switch / add-on opportunity

Undiagnosed

~80%

Drive earlier diagnosis across ATTR-CM patients

1. Global represents US + EU5 + Japan; Sizing estimates based on claims analyses and internal market research (2024), as well as Pfizer public statements; 2. ~40K patients are being actively treated (globally). Recent literature show a range of estimates for many patients experiencing suboptimal response to treatment. In an analysis of US claims/EHR data (Fontana M, et al. data presented at Heart failure Society of America Annual Scientific Meeting 2024), ~50% experienced cardiac worsening (n >800, over median ~ 1 year). 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.

Alnylam

Building on hATTR-PN Leadership to Drive ATTR-CM Launch

The Leader in hATTR-PN

Grew hATTR-PN Category	**>5x** Growth since 2019
Expanded Prescriber Base	**>2x** Growth in HCP prescriber base since 2021
Established Leadership	**>80%** Estimated share of the hATTR-PN category in markets with competition

Teams Expanded – Ready for Launch

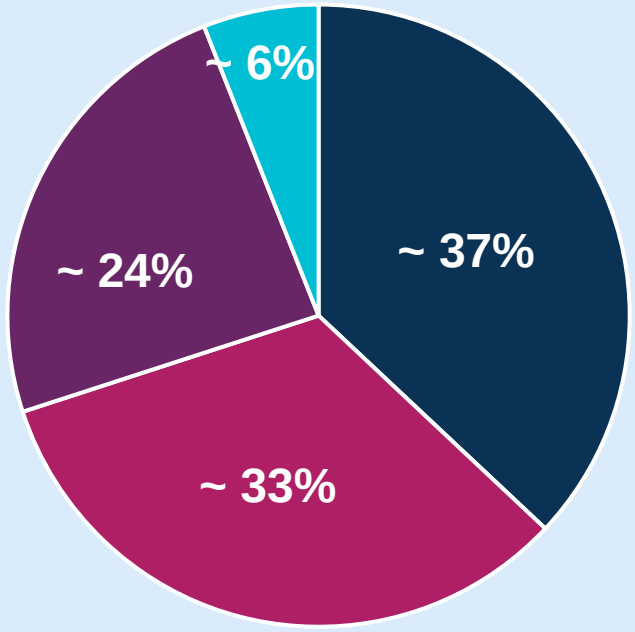
	FROM Today (PN)	**TO** Launch (PN+CM)
 **~3,700** HCPs treating ~95% of patient population	**~65%** **ALNY Coverage** (due to hATTR-PN diagnostic pathways)	**100%** **ALNY Coverage**
 **~170** Health systems accounting for ~80% of potential Rx volume	**~45%** **ALNY Coverage**	**100%** **ALNY Coverage**

Sources (non-exhaustive): Komodo, IQVIA, and Alnylam internal analysis as of Q2 2024

Anticipate Broad Access with Low Patient Out-of-Pocket Costs

Favorable U.S. Coverage for AMVUTTRA in hATTR-PN

Current Payer Mix (U.S.)

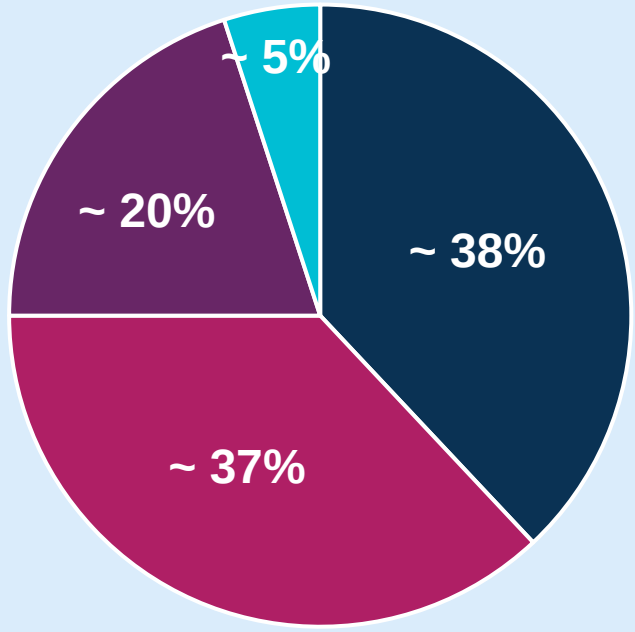


>99%
Coverage[1,2]

~70%
of AMVUTTRA patients today pay **$0** out of pocket

Similar Dynamics Expected in ATTR-CM

Expected Payer Mix (U.S.)



1. Based on DKP PayerScope® data as of August 2024;
2. Payer mix based on Alnylam Assist data

Sources (non-exhaustive): Komodo and Alnylam internal analysis as of Q2 2024. AMVUTTRA is assumed to have a similar payer mix with a majority of coverage under the Medical benefit (i.e. Part B) if approved in ATTR-CM.

■ Medicare Fee for Service ■ Medicare Advantage ■ Commercial ■ Other Government Payers

Multiple Global ATTR-CM Launches Expected in 2025

On Track Toward Early 2025 Launch

- ✓ Submitted sNDA within 90 days of topline results
- ✓ sNDA under Priority Review
- ✓ PDUFA date March 23, 2025

Pursuing Rapid Ex-U.S. Launches

- ✓ Parallel filings achieved in all major regions, including Europe and Japan
- ✓ Priority Review granted in Japan
- ✓ Launches in Germany and Japan expected 2H25

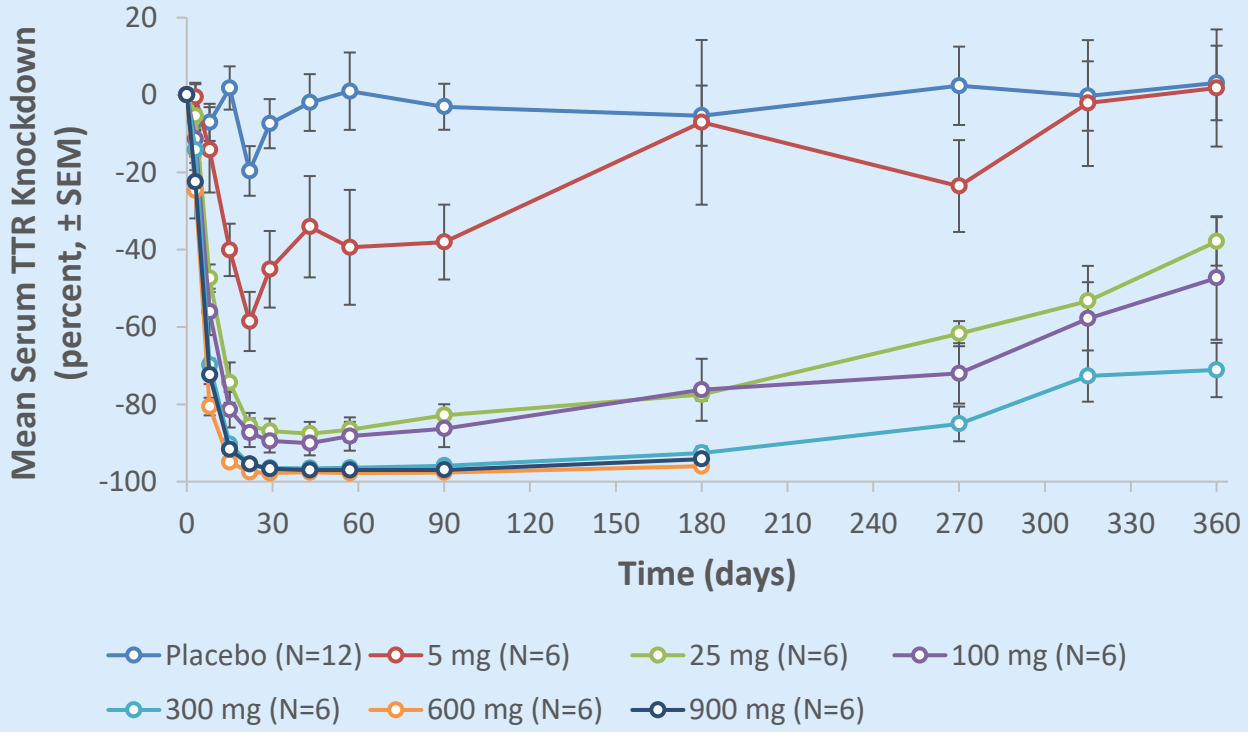
Nucresiran (ALN-TTRsc04) Offers Potential for Best-in-Class Profile

Continued Innovation to Secure Franchise Leadership

Emerging Profile

- ✓ **>95% TTR Knockdown**
- ✓ **Biannual or annual dosing** to optimize patient experience
- ✓ **Encouraging safety** profile to date

Encouraging Phase 1 Data[1]



Phase 3 study initiation in ATTR-CM expected in first half of 2025

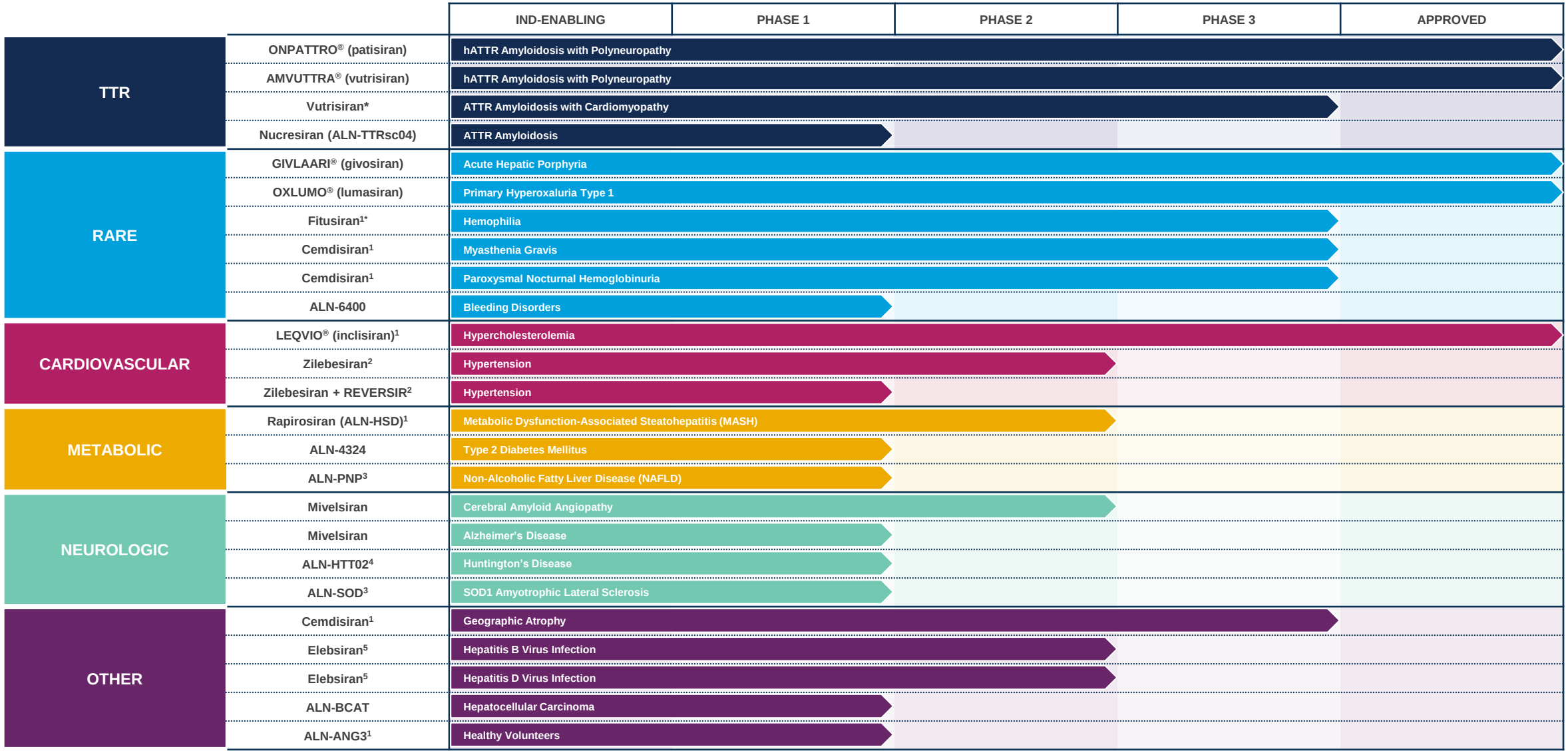
1. Murad et al., AHA 2024

Flagship Franchise for Continued TTR Leadership

- Vutrisiran therapeutic profile supports first-line potential in ATTR-CM
- Focused strategy to expand AMVUTTRA's penetration over time
- Success and strong leadership in hATTR-PN position us to be highly competitive in ATTR-CM
- Favorable market access dynamics expected for vutrisiran
- Multiple global ATTR-CM launches expected in 2025
- Next-gen therapeutic, nucresiran, offers continued innovation for patients

Growth Through Innovation

Robust and High-Value Pipeline of RNAi Therapeutics



** Vutrisiran and fitusiran are under regulatory review. 1 Out-licensed with milestones and/or royalties; 2 Partnered, Alnylam-led development with U.S. profit split and milestones/royalties ex-U.S.; 3 Partner-led with profit split; 4 Partnered, Alnylam-led with profit split; 5 Partner-led with Alnylam option for profit split*

Next Wave of Transformative Medicines Representing Multi-Billion-Dollar Opportunities

Zilebesiran

Transformative Potential for the Treatment of Hypertension

- Potential to reduce CV mortality through continuous control of blood pressure, #1 addressable cause of heart disease
- Over 60 million patients in 7 major markets with uncontrolled hypertension and high CV risk
- Targets AGT with every-6-month subcutaneous dosing regimen
- KARDIA-1 study demonstrated ~15mmHg monotherapy BP reduction[1]

KARDIA-3 Phase 2 results expected 2H 2025; plan to initiate Phase 3 CVOT in 2H 2025

Mivelsiran

Differentiated Approach to Cerebral Amyloid Angiopathy and Alzheimer's Disease

- Potential to reduce strokes in patients with CAA and reduce AD progression
- CAA: Second leading cause of intracerebral hemorrhage, of which there are ~80K in U.S. each year
- Targets APP to lower intra- and extracellular amyloid
- Rapid and robust reductions in Aβ40 and Aβ42 seen in clinic

Phase 1 ongoing in EOAD patients; cAPPricorn-1 Phase 2 study enrolling CAA patients

ALN-HTT02

Bringing Hope to Patients with Huntington's Disease

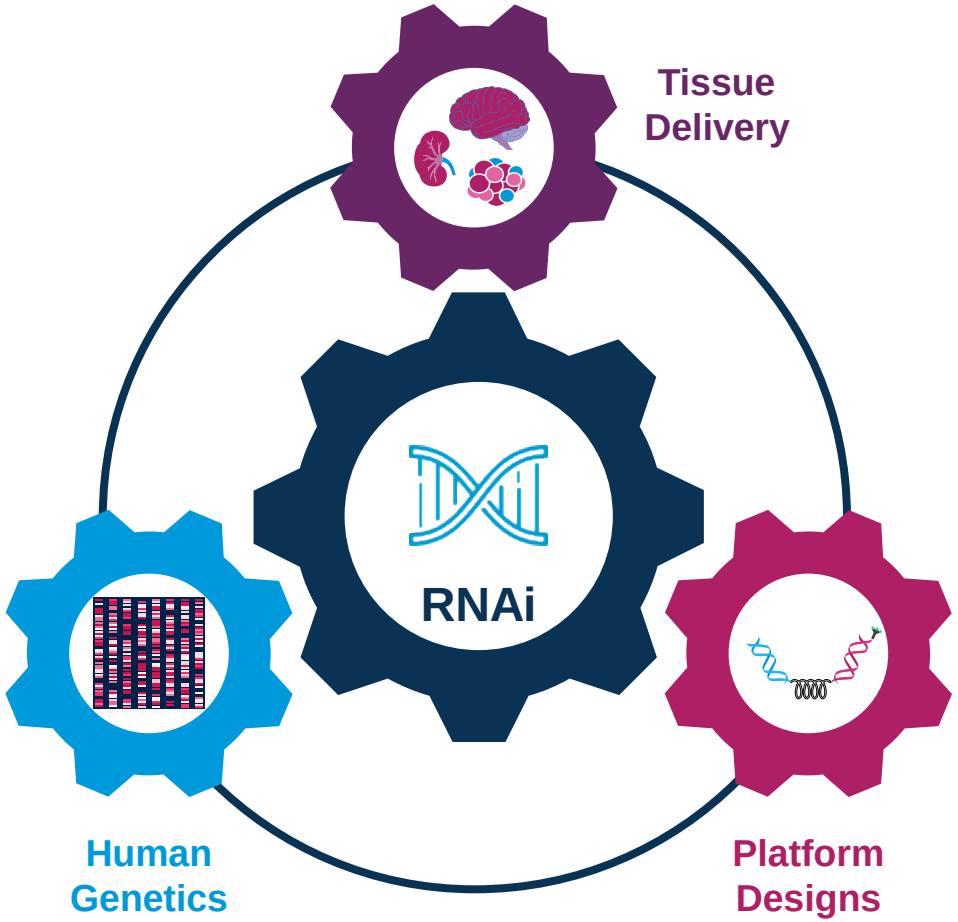
- Potential to prevent widespread neurodegeneration and reduce HD progression
- Most common monogenic neurological disorder in developed countries; >100K symptomatic HD patients globally
- Differentiated exon 1 targeting approach, designed to reduce expression of *all* HTT proteins
- Encouraging pre-clinical data in wild-type NHPs showing deep and sustained HTT lowering, broad CNS distribution, and encouraging safety and tolerability

Phase 1 study enrolling HD patients

1. *Bakris et al., AHA Scientific Sessions 2023*

The Engine Driving Sustainable Innovation

Modular Drug Discovery Platform to Catalyze Long-Term Growth



- Over 25 programs expected in clinic by end of 2025 across four tissue types (liver, CNS, muscle, adipose)
- 4+ CTAs expected per year to drive long-term, sustainable innovation
- Targeting additional tissue types (e.g., heart, kidney, eye)

Alnylam

Strong Financial Performance

2025 Net Product Revenue Guidance Positions Company to Achieve Goal of Sustainable Non-GAAP Profitability

	2025 Guidance
Total TTR Product Sales (PN & CM*) (ONPATTRO, AMVUTTRA)	$1,600 to $1,725 million
Total Rare Product Sales (GIVLAARI, OXLUMO)	$450 to $525 million
Total Combined Product Sales	**$2,050 to $2,250 million**
Non-GAAP Operating Income	**Achieve profitability**

Note: Additional financial guidance, including collaboration and royalty revenue and GAAP and non-GAAP combined R&D and SG&A expenses, will be provided on Alnylam's year-end earnings call in February 2025.

** Guidance assumes FDA approval of the sNDA for vutrisiran for the treatment of adults with ATTR amyloidosis with cardiomyopathy by the March 23, 2025 PDUFA target action date.*

Alnylam 2025 Goals

onpattro (patisiran) amvuttra (vutrisiran) GIVLAARI (givosiran) OXLUMO (lumasiran)		Combined Net Product Revenue Guidance $2,050M – $2,250M	**2025**
VUTRISIRAN	ATTR Amyloidosis	U.S. FDA Approval	**PDUFA date March 23, 2025**
		Additional Global Approvals (Japan, EU)	**Q2, Q3**
NUCRESIRAN* (ALN-TTRsc04)	ATTR Amyloidosis	Initiate Phase 3 Study in ATTR-CM	**H1**
ZILEBESIRAN*	Hypertension	KARDIA-3 Phase 2 Results	**H2**
		Initiate Phase 3 CVOT	**H2**
MIVELSIRAN*	Cerebral Amyloid Angiopathy and Alzheimer's Disease	Interim Phase 1 Part B Data in EOAD	**H2**
		Initiate Phase 2 Study in AD	**H2**
ALN-6400*	Bleeding Disorders	Initiate Phase 2 Study	**H2**
ADDITIONAL PROGRAMS		File ≥4 New INDs	**2025**
KEY PARTNER-LED PROGRAM MILESTONES			
FITUSIRAN* (Sanofi)	Hemophilia	U.S. FDA Approval	**PDUFA date March 28, 2025**
ELEBSIRAN* (Vir)	Chronic HBV/HDV	Initiate Phase 3 study in HDV	**H1**
		Phase 2 HBV Functional Cure Results	**Q2**
CEMDISIRAN* (Regeneron)	Complement-Mediated Diseases	Phase 3 MG Results	**H2**

** Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established.*
EOAD = Early Onset Alzheimer's Disease; MG = Myasthenia Gravis

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Alnylam 2025 Goals

onpattro (patisiran) amvuttra (vutrisiran) GIVLAARI (givosiran) OXLUMO (lumasiran)		Combined Net Product Revenue Guidance $2,050M – $2,250M	2025
VUTRISIRAN	ATTR Amyloidosis	U.S. FDA Approval	PDUFA date March 23, 2025
			Q2, Q3
NUCRESIRAN* (ALN-TTRsc04)			H1
ZILEBESIRAN*			H2
			H2
MIVELSIRAN*			H2
			H2
ALN-6400*			H2
ADDITION			2025
FITUSIRAN* (Sanofi)			PDUFA date March 28, 2025
ELEBSIRAN* (Vir)	Chronic HBV/HDV	Initiate Phase 3 study in HDV	H1
		Phase 2 HBV Functional Cure Results	Q2
CEMDISIRAN* (Regeneron)	Complement-Mediated Diseases	Phase 3 MG Results	H2

6 **commercial products**
(4 WHOLLY OWNED)

2 **Phase 3 study starts**

Vutrisiran launch in ATTR-CM

≥4 **new INDs**

KARDIA-3
Phase 2 results

Achieve sustainable non-GAAP profitability

** Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established.*
EOAD = Early Onset Alzheimer's Disease; MG = Myasthenia Gravis

Alnylam

Strong Progress Against Ambitious Five-Year Goals

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; 10+ in late stages; 4+ INDs per year

PERFORMANCE: ≥40% revenue CAGR through YE 2025

PROFITABILITY: Achieve sustainable non-GAAP profitability within period

Alnylam


Silence disease
Amplify life™
Alnylam®