



42nd Annual J.P. Morgan Healthcare Conference

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Chief Executive Officer

January 8, 2024

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, expectations regarding Alnylam's aspiration to become a top-tier biotech company and the planned achievement of its "*Alnylam P⁵x25*" strategy, the potential for Alnylam to identify new potential drug development candidates and advance its research and development programs, Alnylam's ability to obtain approval for new commercial products or additional indications for its existing products, and Alnylam's projected commercial and financial performance, 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 P⁵x25*" strategy; 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, including topline results from the Company's HELIOS-B Phase 3 study of vutrisiran; 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 in the future; 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; the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on Alnylam's business, results of operations and financial condition and the effectiveness or timeliness of Alnylam's efforts to mitigate the impact of the pandemic; 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.

Leader in RNAi Therapeutics

On Track to Become Top-Tier, Self-Sustainable Biotech by End of 2025



OUTSTANDING R&D PRODUCTIVITY

- Validated new class of medicines
- **5** medicines approved in < 4 years



LEADING COMMERCIAL CAPABILITIES

- **>\$1 BILLION** generated in annual product sales
- **>60** countries with commercial presence through direct or distributor sales



ROBUST AND HIGH-YIELDING PIPELINE

- **15** clinical programs across rare, specialty, and prevalent diseases
- Up to **15** additional programs expected in clinic by end of 2025



STRONG FINANCIAL POSITION

- **>\$2 BILLION** cash balance
- On path toward financial self-sustainability

2023 Delivered Strong Progress Across the Business

Driving Robust Product Growth



Combined net product revenues of
\$1,241 million*
(39% growth YoY)

Over
5,000
patients on Alnylam
commercial medicines

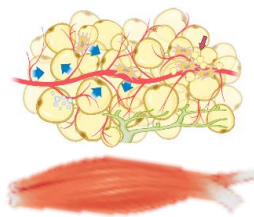
Extending RNAi Leadership



Human Proof of Concept for
RNAi therapeutics in CNS

KARDIA₁

Positive **zilebesiran** Phase 2 results in
patients with mild-to-moderate hypertension



Preclinical delivery to
new tissue types
(adipose and muscle)

55 medical publications, including
14 in high-impact[^] journals



The NEW ENGLAND
JOURNAL of MEDICINE

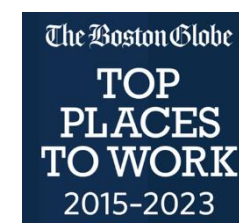
nature

Building a Sustainable Business

Landmark partnership to
maximize global opportunity for
zilebesiran in hypertension



Maintained strong financial position
\$2.4 billion in cash
at year-end 2023*



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 2024. ^ Defined as Impact Factor (IF) > 10.

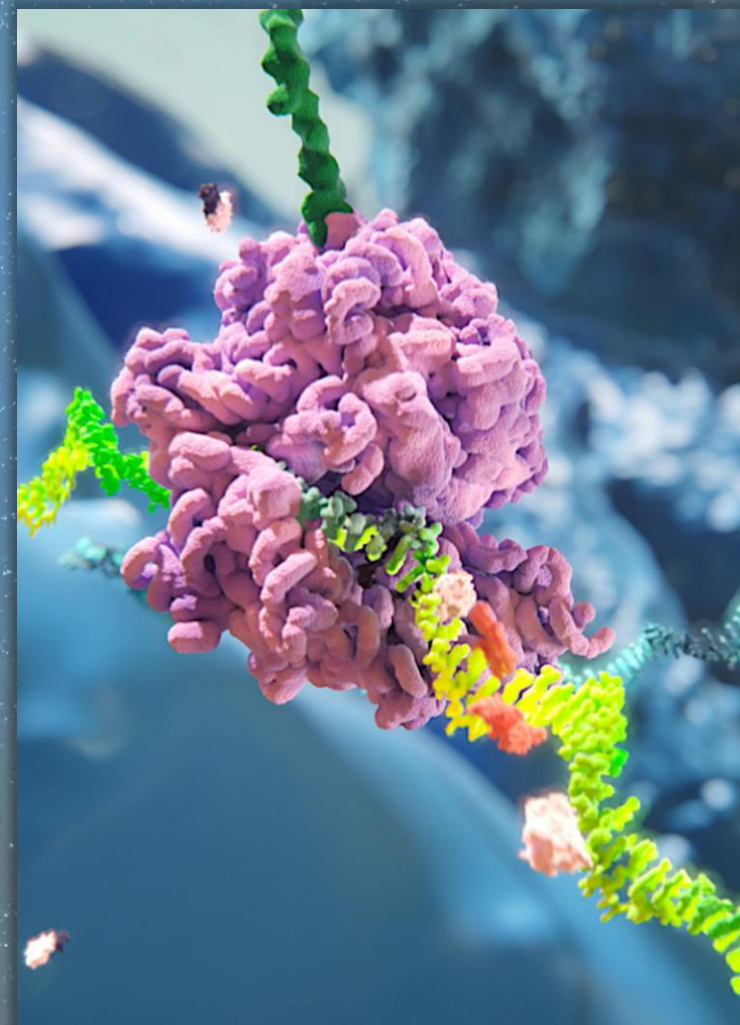


Chen
Living with hATTR Amyloidosis (Brazil)

**STRONG COMMERCIAL
GROWTH**



**ROBUST & HIGH-YIELD
R&D PIPELINE**



**SUSTAINABLE
INNOVATION ENGINE**

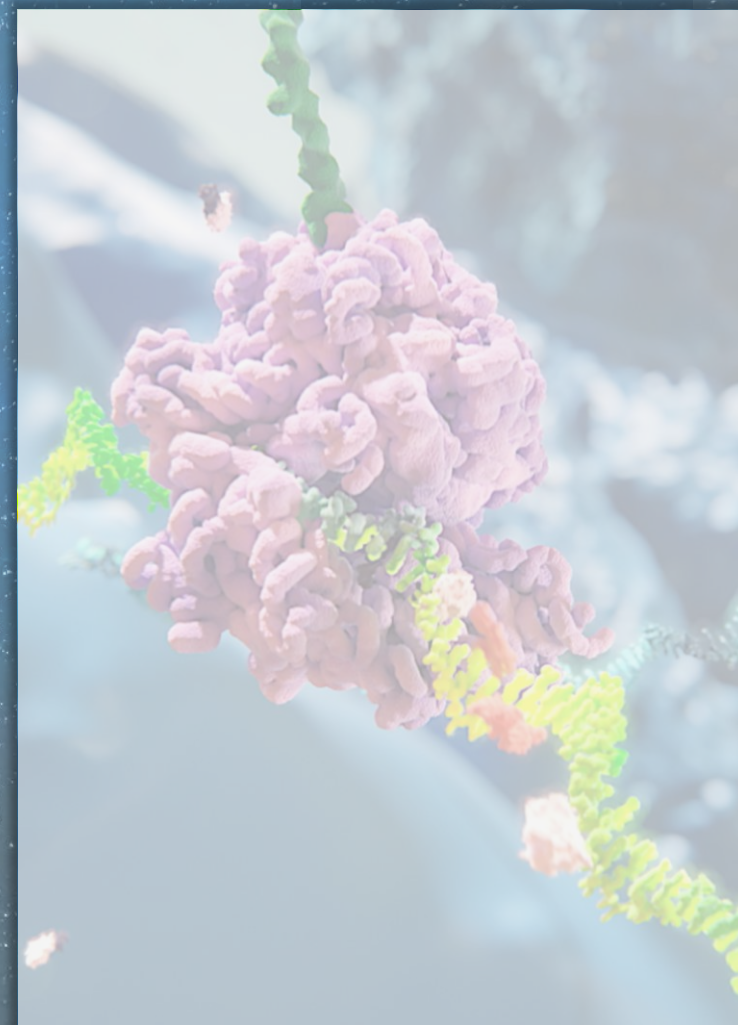


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**STRONG COMMERCIAL
GROWTH**



**ROBUST & HIGH-YIELD
R&D PIPELINE**



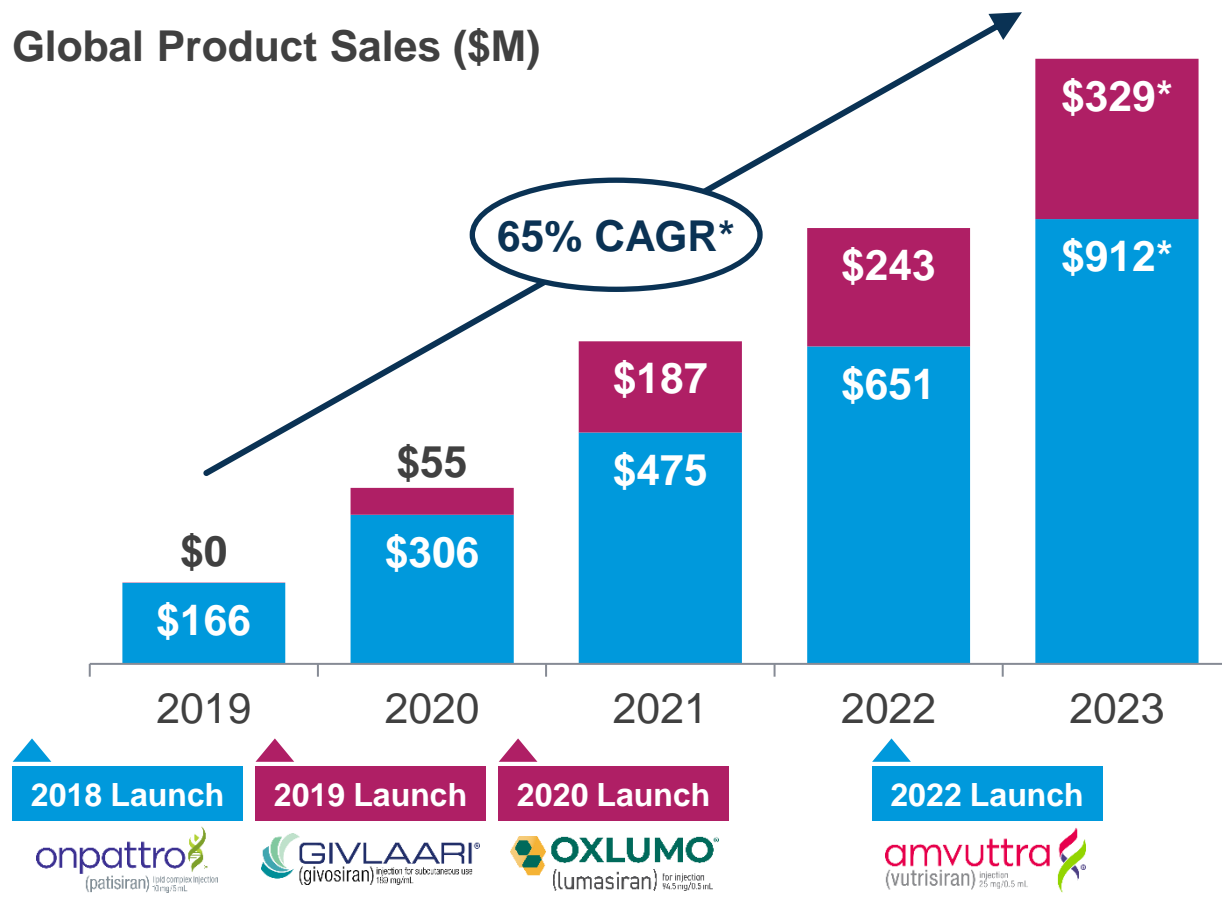
**SUSTAINABLE
INNOVATION ENGINE**

Strong Commercial Performance, Well Positioned for Exceptional Growth

Transformational Medicines Delivering \$1,241 Million in Annual Product Revenues in 2023*

Robust 39% 2023 YoY Growth* in Total Net Product Revenues

Global Product Sales (\$M)



TTR Franchise

40%*

YoY growth in TTR franchise revenues

>4,060

Patients in TTR franchise globally

Ultra-Rare Franchise

35%*

YoY growth in ultra-rare franchise revenues

>1,080

Patients in ultra-rare franchise globally

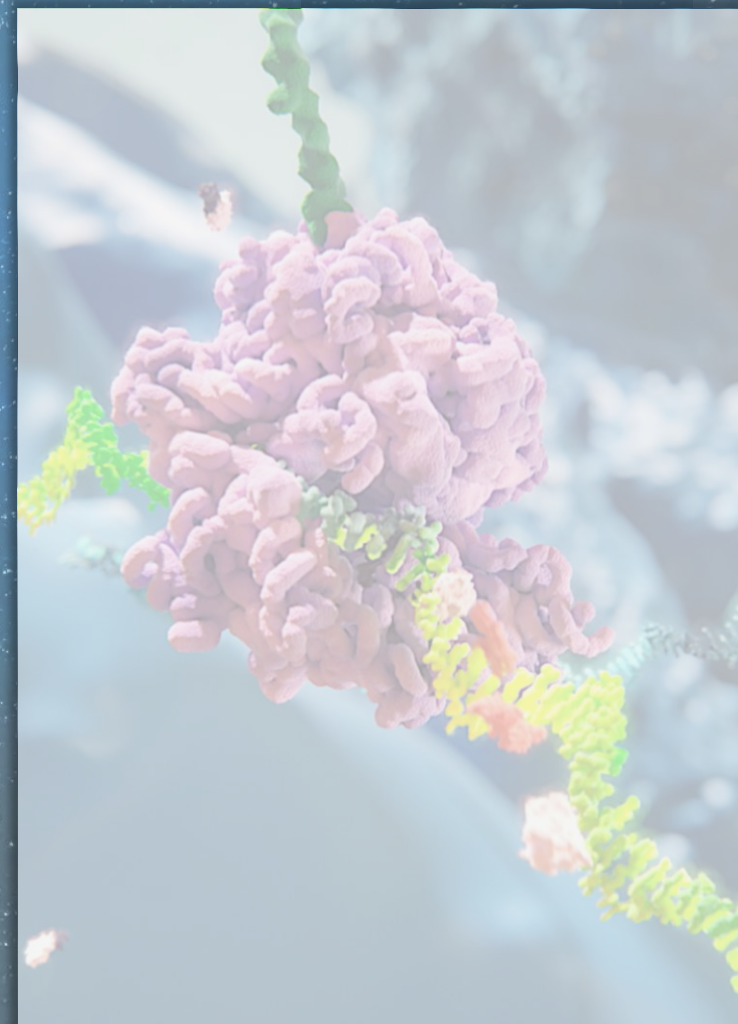


Chen
Living with hATTR Amyloidosis (Brazil)

**STRONG COMMERCIAL
GROWTH**








**ROBUST & HIGH-YIELD
R&D PIPELINE**



**SUSTAINABLE
INNOVATION ENGINE**

Advancing a Robust and High-Yielding Pipeline of RNAi Therapeutics

Positioned to Deliver Strong Growth and Innovation Across Multiple Disease Areas and Indications

IND-enabling	Phase 1	Phase 2	Phase 3	Approved
ALN-HTT02* Huntington's Disease	ALN-TTRsc04 ATTR Amyloidosis	Zilebesiran* Hypertension	Vutrisiran ATTR Amyloidosis with CM	 onpattro (patisirán) lipid complex injection 10 mg/5 mL
ALN-SOD1‡ Amyotrophic Lateral Sclerosis	ALN-KHK Type 2 Diabetes Mellitus	ALN-HSD^ NASH	Fitusiran^ Hemophilia	 amvuttra (vutrisiran) injection 25 mg/0.5 mL
ALN-Gene A Bleeding Disorders	ALN-APP* Alzheimer's Disease	Elebsiran‡ (ALN-HBV02/VIR-2218) Hepatitis B Virus Infection	Cemdisiran (pozelimab combo)^ Myasthenia Gravis	 GIVLAARI (givosiran) injection for subcutaneous use 189 mg/mL
ALN-Gene Y Type 2 Diabetes Mellitus	ALN-PNP† NASH	Elebsiran‡ (ALN-HBV02/VIR-2218) Hepatitis D Virus Infection	Cemdisiran (pozelimab combo)^ Paroxysmal Nocturnal Hemoglobinuria	 OXLUMO (lumasiran) for injection 94.5 mg/0.5 mL
	ALN-BCAT Hepatocellular Carcinoma	Belcesiran^ Alpha-1 Liver Disease		 LEQVIO (inclisiran) injection 284 mg/1.5 mL
		ALN-APP* Cerebral Amyloid Angiopathy		

* Partnered, Alnylam-led with profit split † Partner-led with profit split ‡ Partner-led with Alnylam option for profit split ^ Partner-led with Milestones/Royalties
ALN-APP is awaiting CTA approval to begin Phase 2 in CAA

ATTR Amyloidosis

Rare, Progressively Debilitating, and Fatal Disease

Description

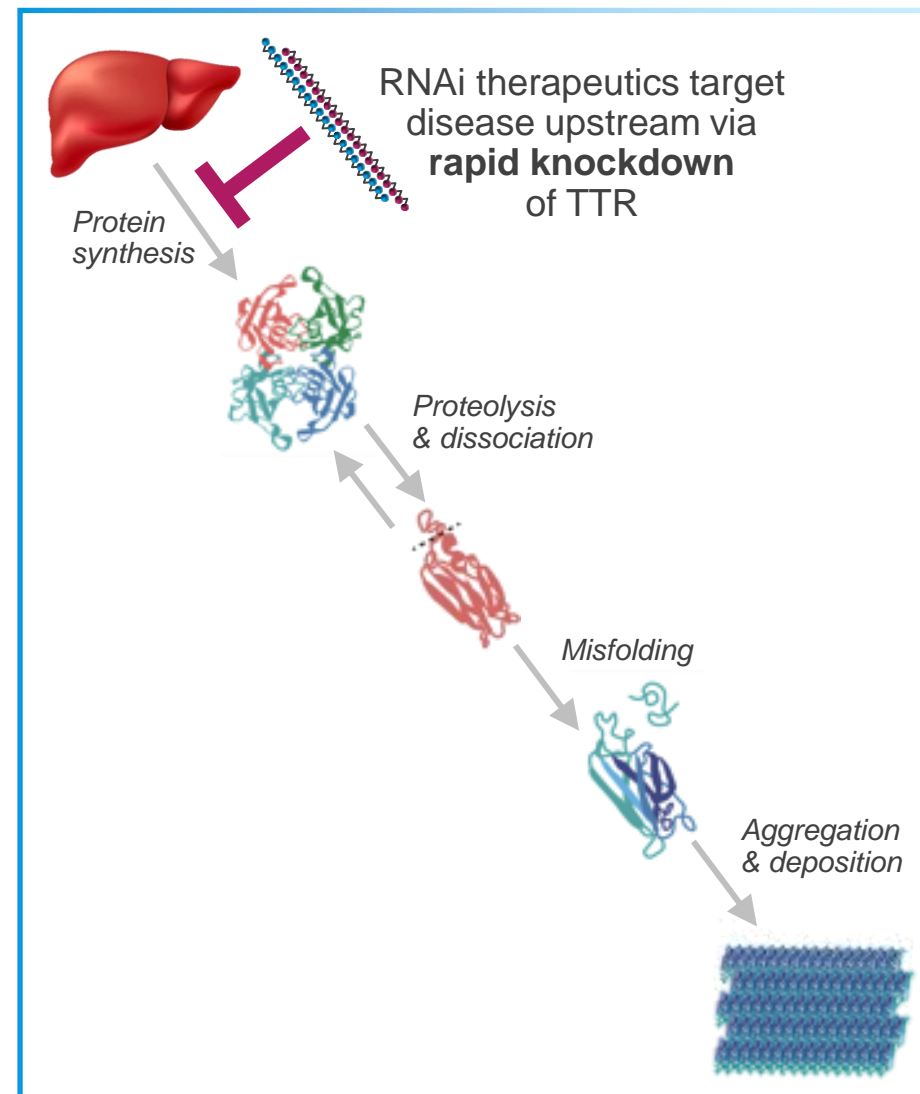
Caused by a misfolded transthyretin (TTR) protein that accumulates as amyloid deposits in multiple tissues including heart, nerves, and GI tract¹

Hereditary ATTR (hATTR) Amyloidosis

~50,000
patients worldwide²

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000–300,000
patients worldwide³



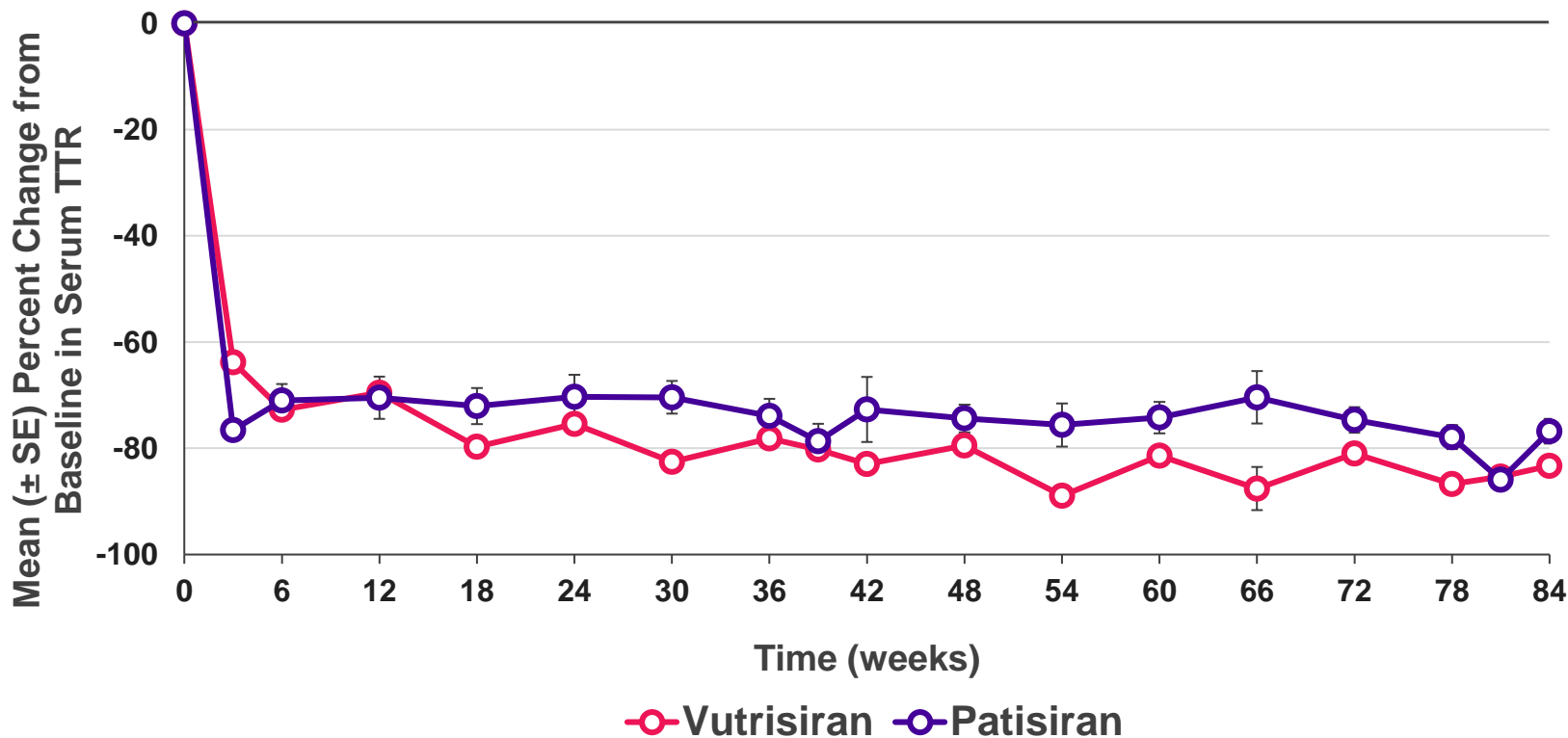
1. Coelho T, et al. *N Engl J Med*. 2013;369(9):819-829

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

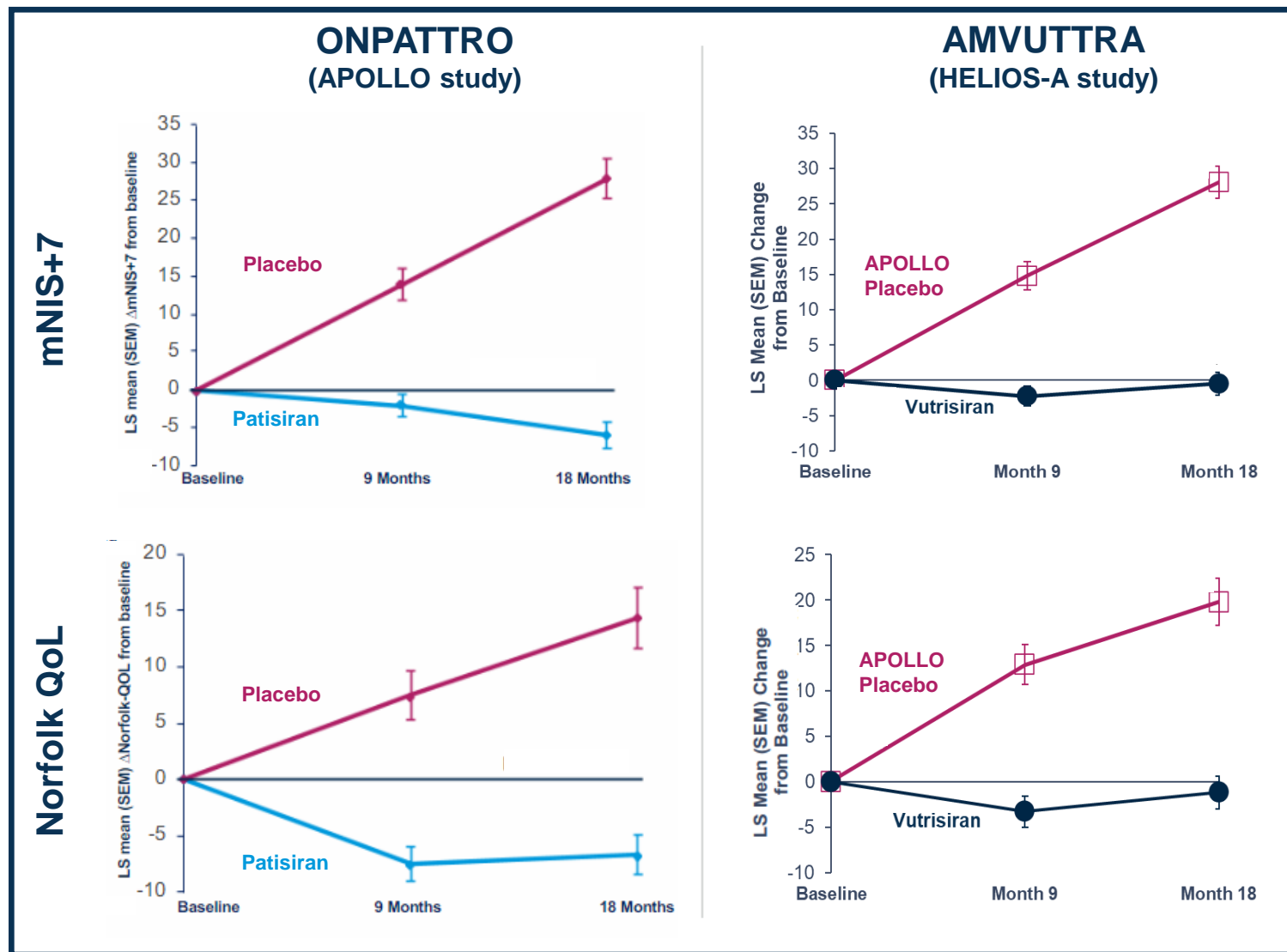
RNAi Therapeutics Deliver Rapid Knockdown of Disease-Causing TTR Protein

Change from Baseline in Serum TTR Levels*



- TTR deposition in tissue of ATTR patients causes irreversible damage and premature death¹
- RNAi mechanism drives **rapid knockdown** of TTR
- Majority of HCPs say that speed of reaching 80% mean serum TTR reduction impacts treatment consideration²

Rapid Knockdown Results in Transformative Profile in hATTR Amyloidosis with Polyneuropathy



Strong Commercial Uptake

GROWTH

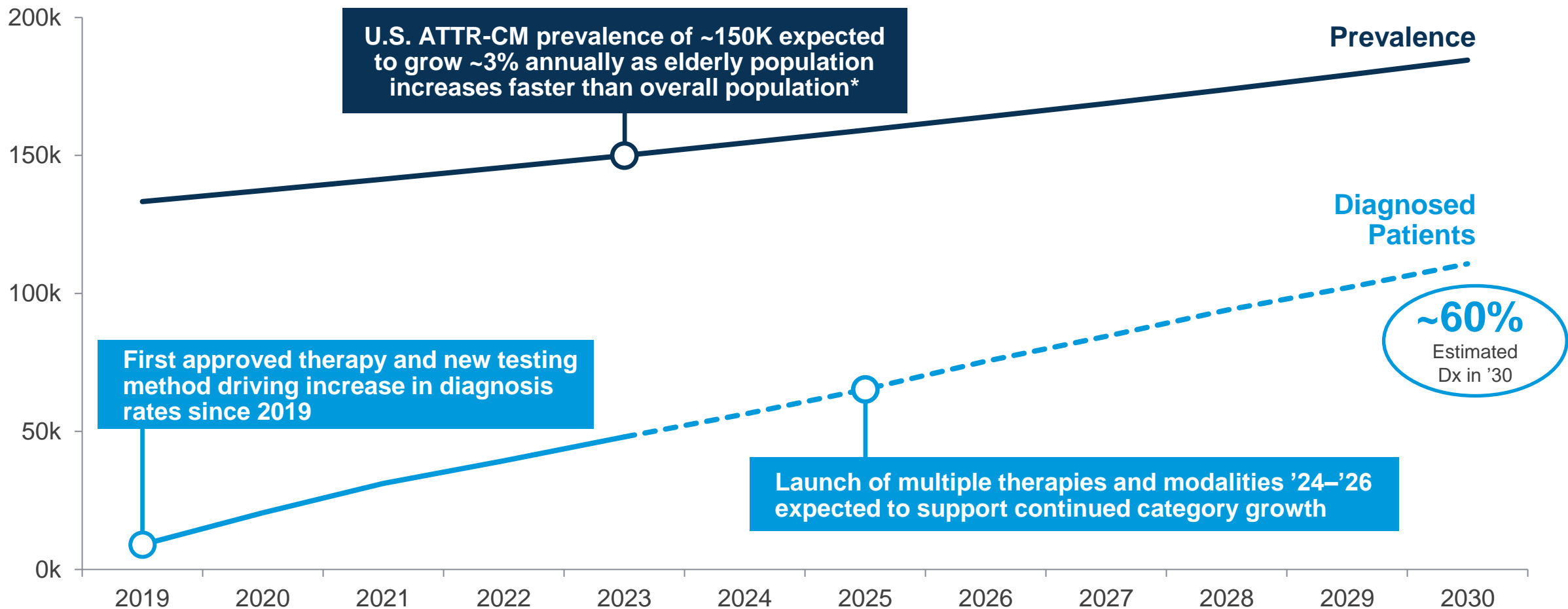
- Approaching \$1 billion in annual revenues
- >4,060 patients on commercial ONPATTRO or AMVUTTRA globally

LEADERSHIP

- >90% estimated U.S. market share
- >80% estimated market share in Japan and Europe

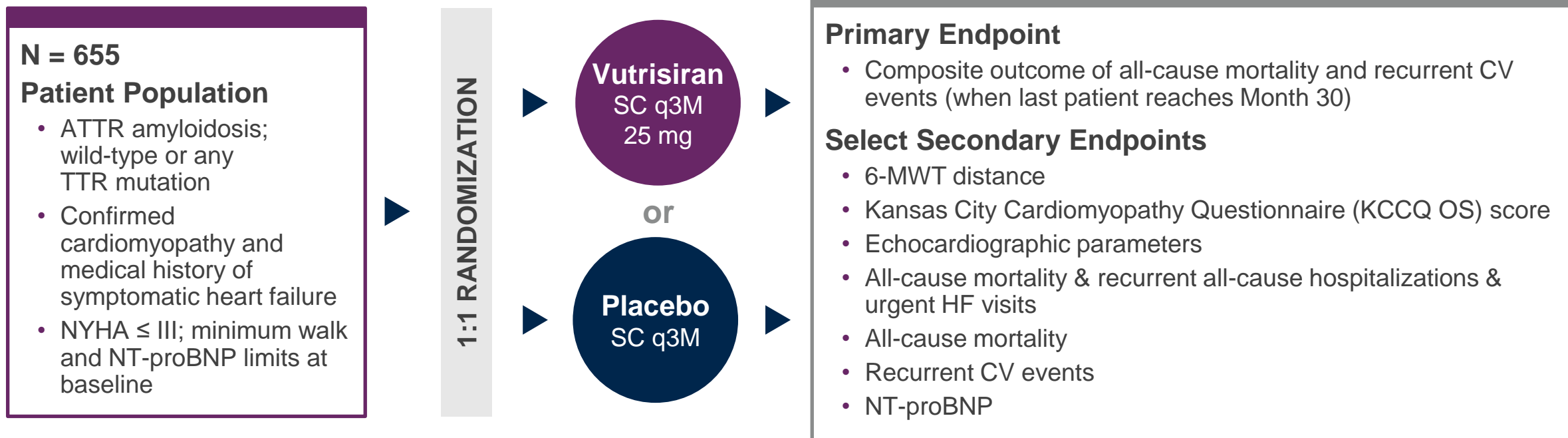
Exceptional Growth Potential in ATTR-CM Market

of U.S. ATTR-CM Patients



Vutrisiran **HELIOS·B** Phase 3 Study

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

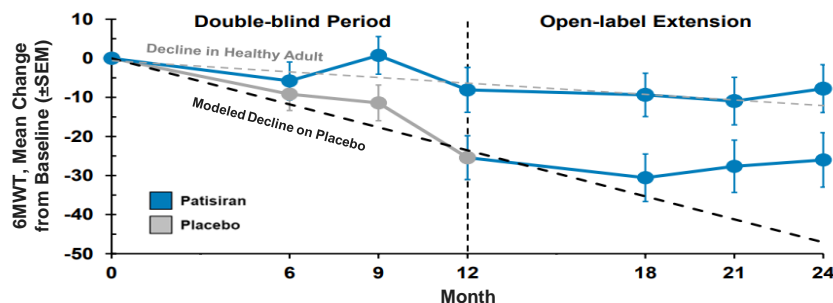


Topline results expected **early 2024**

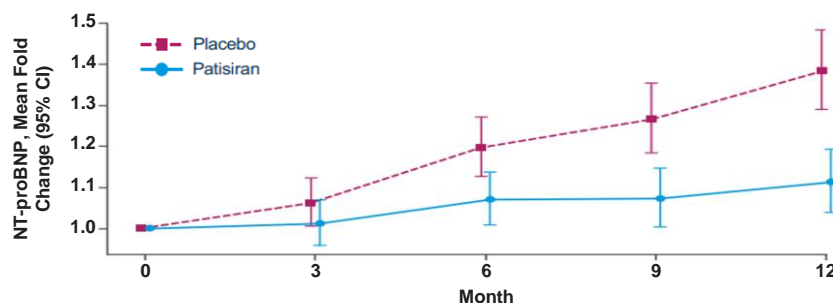
HELIOS·B Positioned to Deliver Outcomes Benefit in ATTR-CM

Supportive Data from Patisiran in APOLLO-B

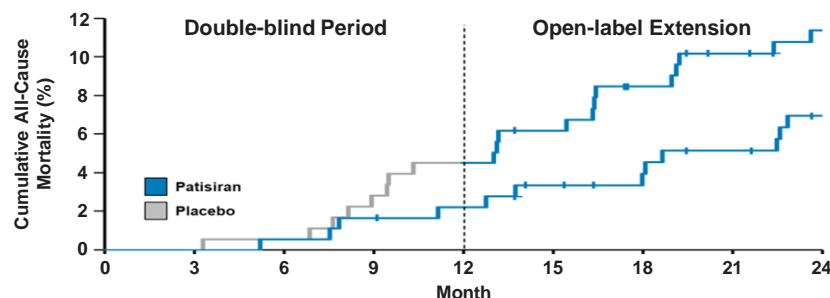
Evidence for Disease Stabilization



Reduction in Disease Biomarkers



Early Separation of Mortality Curves



Design

- Designed and powered to deliver **outcomes**; ~2x as large and ~3x as long as APOLLO-B
- Enriched for patients most likely to benefit, excluding advanced NYHA III and IV
- Longest follow-up of any ATTR-CM study (36 months in most patients)
- Analyses planned to demonstrate **consistency of effect across key subgroups**

Execution

- Overenrolled by ~10%
- Tafamidis baseline subgroup **lower than target of 50%**
- Low rate of tafamidis drop-ins, well within expectations

If Approved, Vutrisiran Expected to Have Market-Leading Profile in ATTR-CM

Majority of HCPs say that **speed of reaching 80% mean serum TTR reduction** impacts treatment consideration¹

HCPs report that **~75% of patients** treated with tafamidis have only **partial or no response**²

Nearly **twice as many patients** indicated they would **prefer quarterly HCP-administration** vs. monthly self-administration³



Unique MOA

- Highly **targeted RNAi-based mechanism** enables **rapid knockdown** of TTR
- Reduces pathogenic protein production, acting **upstream of approved medicines**



Potential for Impactful Clinical Profile

- Reduction in **mortality** and **CV hospitalizations**
- Halting decline in **functional capacity** and **quality of life**
- **Well tolerated safety profile**



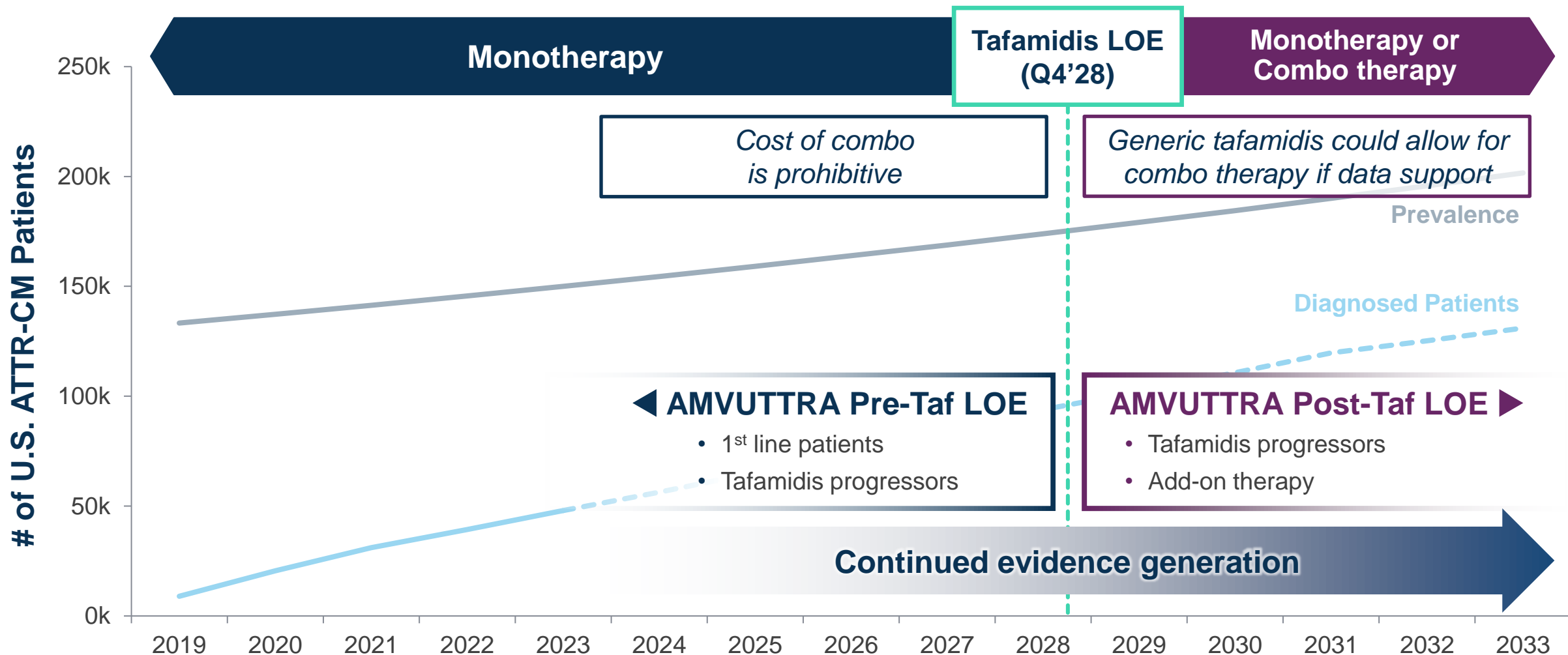
Only 4 Doses per Year

- **Quarterly dosing** that aligns with doctor visits and promotes strong adherence

1. Market research with U.S. HCPs (n=40). 2. Market research with HCPs (n=530). 3. Market research with ATTR patients (n=205).

Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of the cardiomyopathy of ATTR have not been established or evaluated by the FDA, EMA or any other health authority. The information is intended to provide an overview of the potential clinical profile of vutrisiran in ATTR-CM

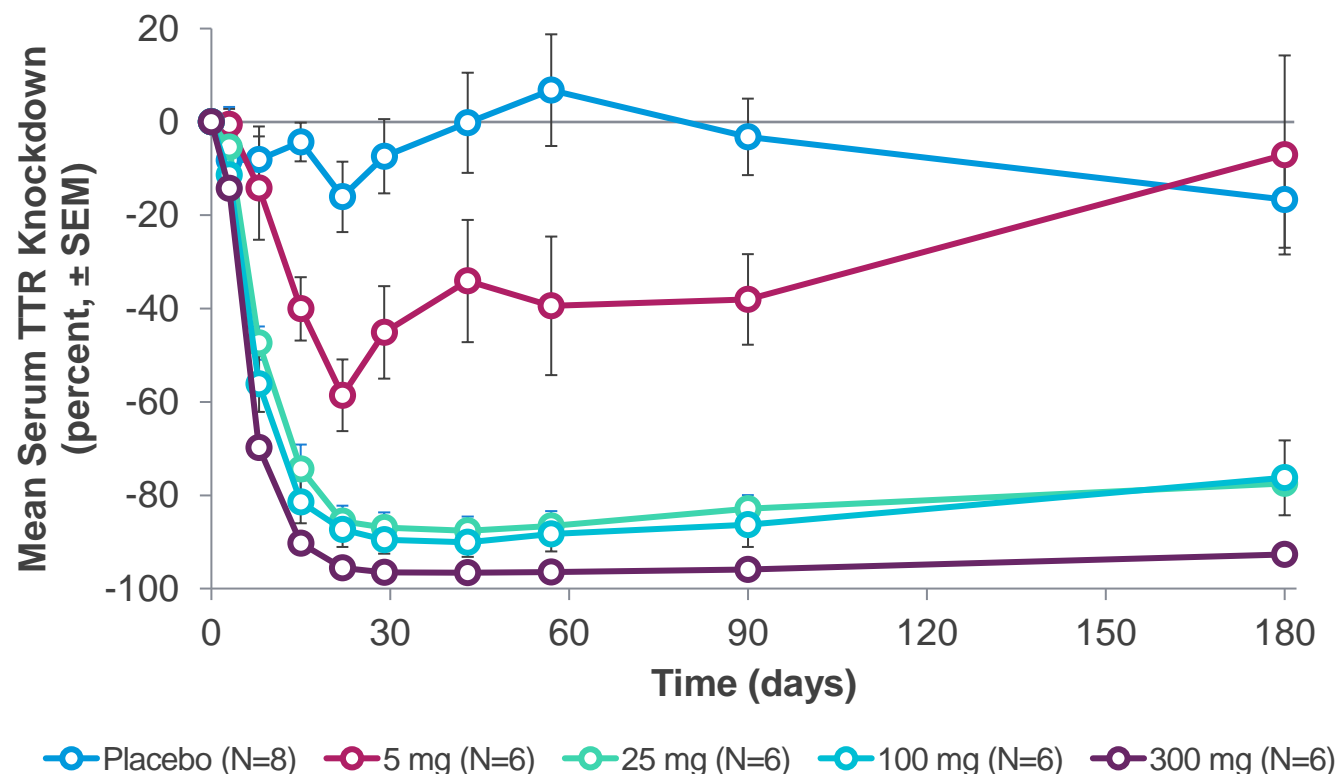
Profile of Vutrisiran Expected to Support First-Line Positioning in ATTR-CM



Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of the cardiomyopathy of ATTR have not been established or evaluated by the FDA, EMA or any other health authority. Pending positive HELIOS-B study results and regulatory approval.
Source: Internal Market research. LOE: loss of exclusivity.

Expanding TTR Leadership with ALN-TTRsc04

Initial Phase 1 Results Support Best-in-Class Profile



- Single 300mg dose resulted in **rapid, deep, and durable knockdown** of serum TTR:
 - **>90%** at Day 15
 - **97%** at Day 29
 - **93%** at Day 180
- All doses of ALN-TTRsc04 **well tolerated** to date; no adverse events considered related to study drug by investigator
- Data support **potential for annual subcutaneous dosing**

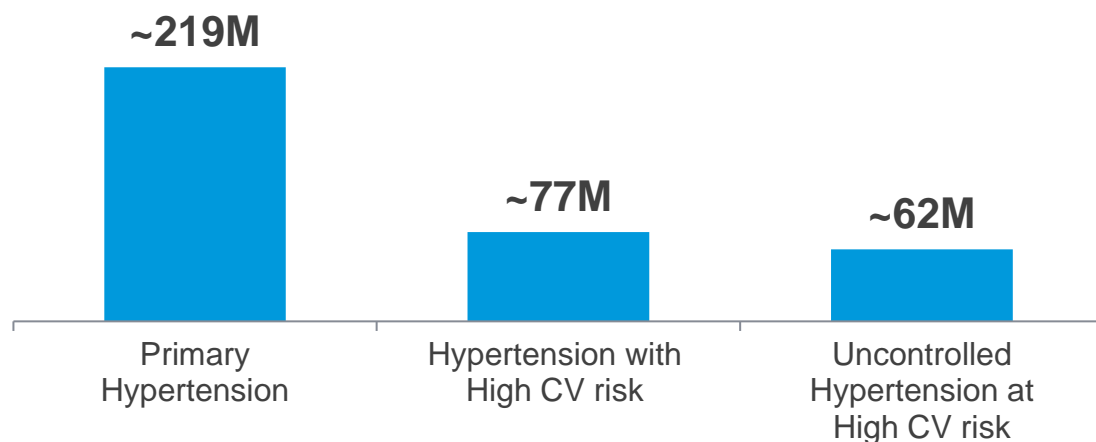
Phase 1 study ongoing

Phase 3 study initiation in ATTR-CM expected **at or around year-end 2024**

Uncontrolled Hypertension is a Global Health Crisis

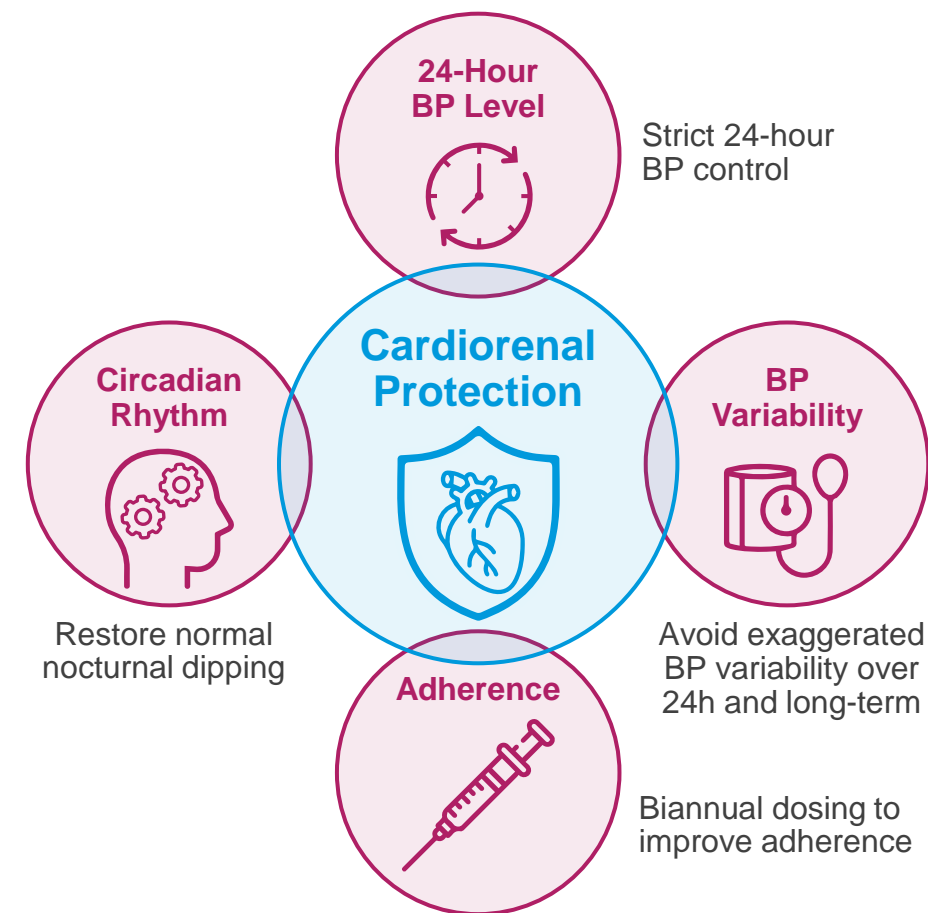
Leading Preventable Risk Factor for Cardiovascular Morbidity and Mortality

Number of Patients
(7 Major Markets)



	Risk Reduction per 10 mm Hg Decrease in SBP*
Major CV Events	20%
CHD	17%
Stroke	27%
HF	28%
Renal Failure	5%
All Cause Mortality	13%

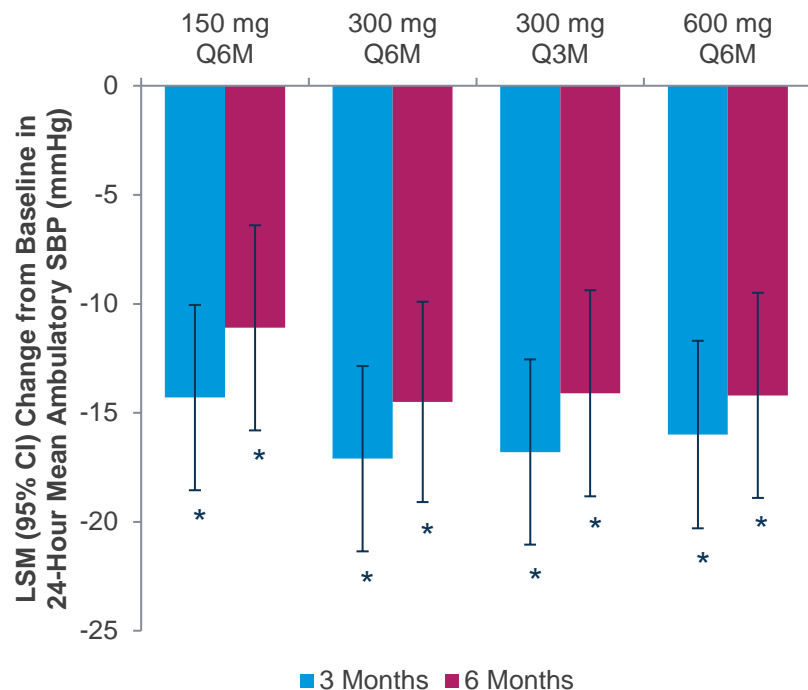
Targeting Tonic BP Control to Reduce Cardiovascular and Renal Risks



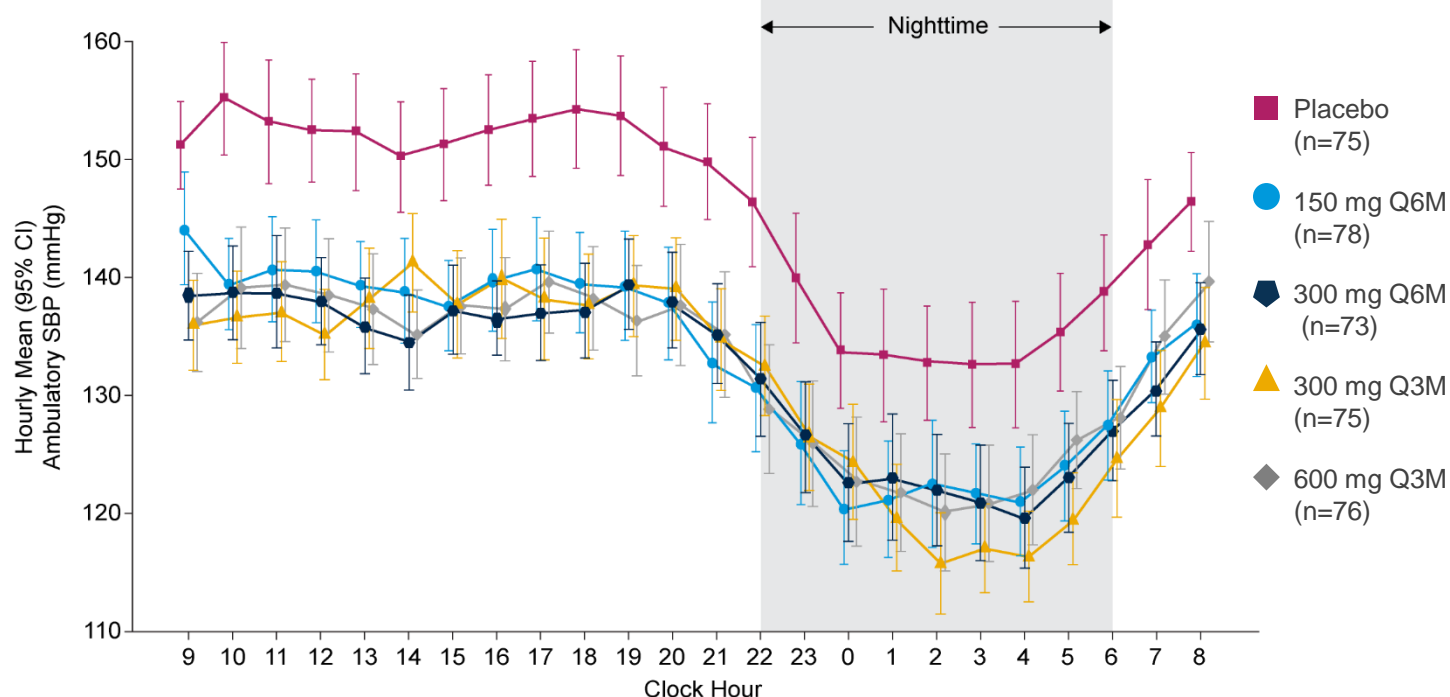
Zilebesiran Data Support Potential to Transform Treatment of Hypertension

KARDIA¹ Phase 2 Results: Single Doses Reduced Blood Pressure Out to Six Months

Robust 24-hour Mean SBP Reduction



24-hour Tonic BP Control Maintained Out to Month 6

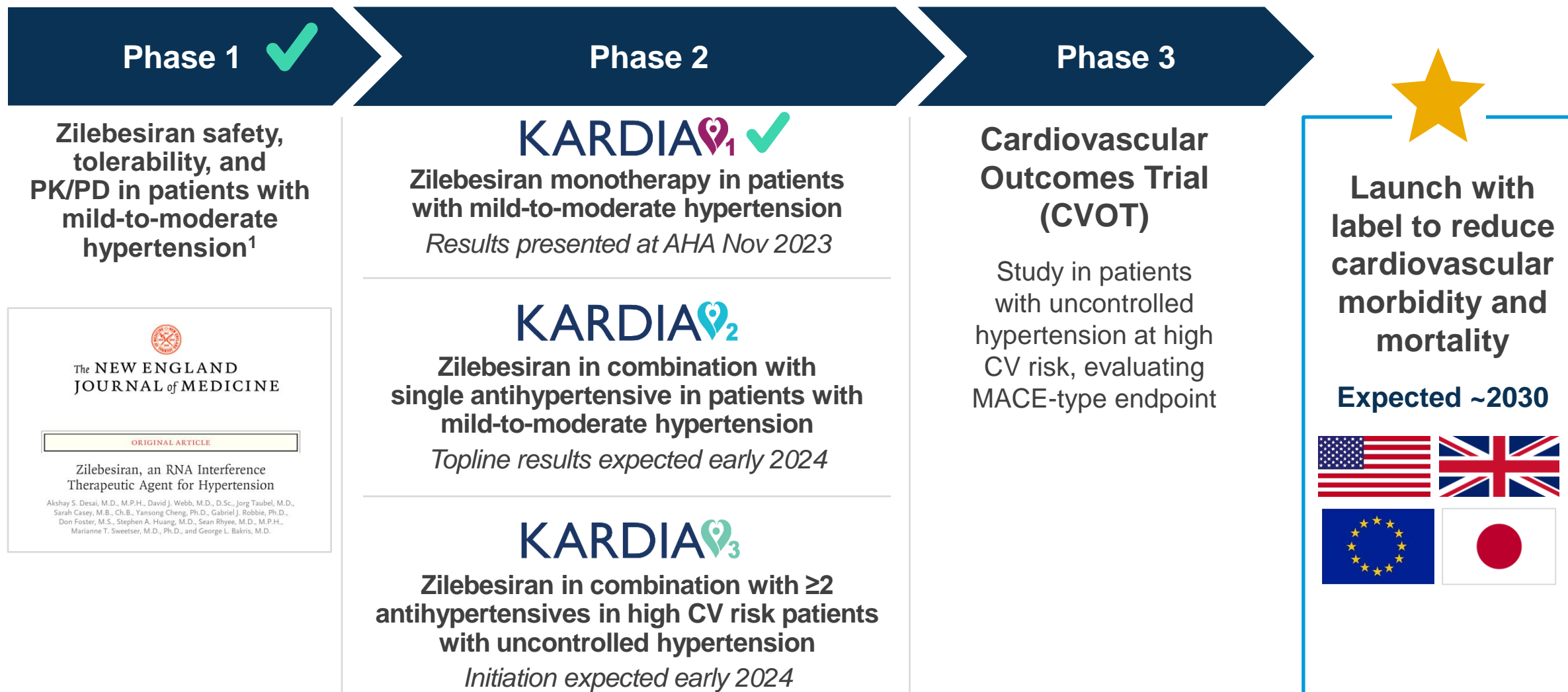


- Generally well tolerated
- Low incidence of AEs of ISR, hyperkalemia, and hypotension, which were mild or moderate in severity and transient; most did not require therapeutic intervention

* $p < 0.0001$; Blood pressure assessments were censored if taken while patients were receiving or within 2 weeks after stopping any rescue medication. Data points are staggered for visualization; Zilebesiran is an investigational RNAi therapeutic for the treatment of hypertension; 1. Bakris et al. AHA Scientific Sessions 2023; ^a Adjusted 95% CIs and p values for the Month 3 primary analysis are based on Dunnett's test; BL, baseline; CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure; AEs, adverse events; ISR, injection site reaction.

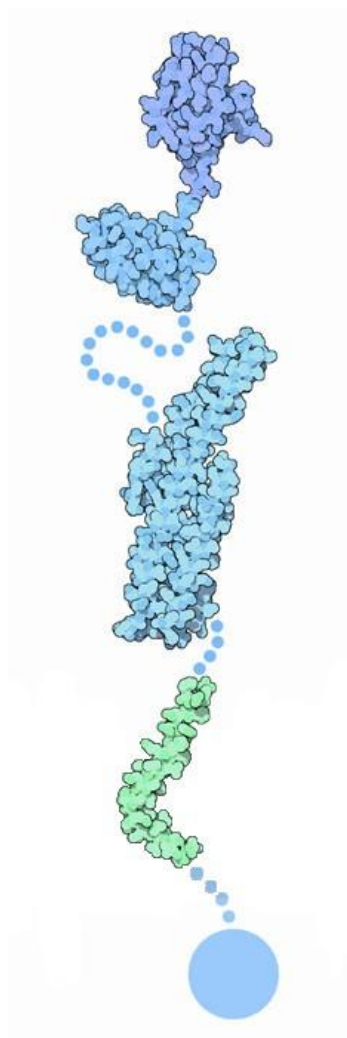
Exploring Benefits of Tonic BP Control to Reduce CV Risk

Comprehensive Zilebesiran Development Plan to Reimagine Treatment of Hypertension



Expanding Beyond Liver with First CNS Program in Clinic

ALN-APP Has Potential to Address Multiple Patient Populations with High Unmet Need



APP: One target, two distinct pathological processes

- ☑ Genetically validated target for CAA and AD
- ☑ Upstream of A β 42 and A β 40, pathogenic proteins involved in CAA and AD
- ☑ Significant patient population with high unmet need in both diseases
 - CAA: Second leading cause of intracerebral hemorrhage
 - AD: Over 5M people affected in U.S. (over 30M worldwide)



Cerebral Amyloid Angiopathy (CAA)

- APP mutations cause hereditary CAA
- Amyloid deposits in walls of vessels in CNS and results in cerebral hemorrhages and cognitive impairment



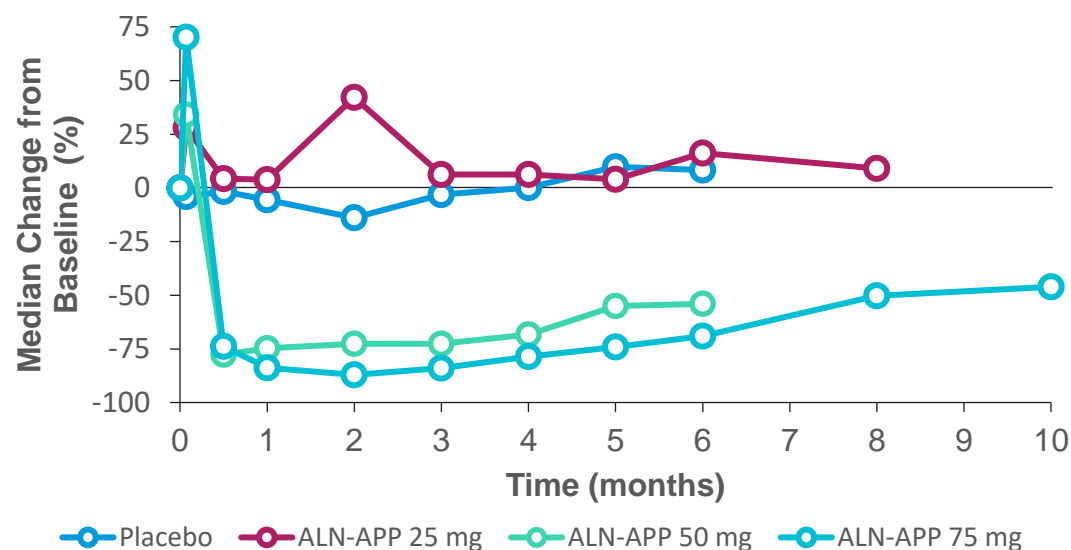
Alzheimer's Disease (AD)

- APP mutations and duplications cause Early Onset AD
- Amyloid deposits in brain tissue, tau tangles in neurons, neurodegeneration

ALN-APP Achieved Rapid and Durable Reductions in Key Biomarkers

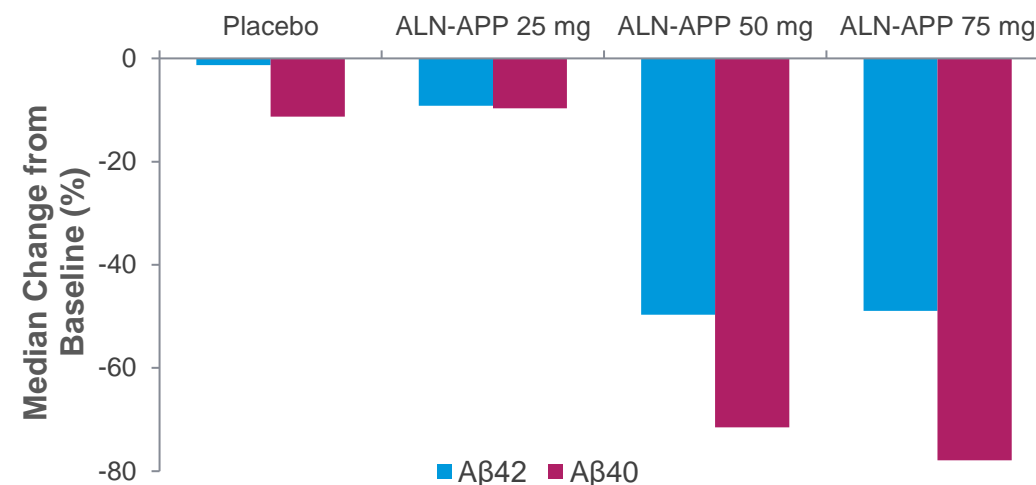
Phase 1 Results* Mark First Demonstration of Gene Silencing by RNAi Therapeutics in Human Brain

Rapid and Durable Reductions in CSF sAPP β



- Generally well tolerated
- AEs generally mild to moderate in severity; most unrelated to study drug
- CSF safety biomarkers, routine lab assessments, and preliminary data for exploratory biomarker neurofilament light chain (NfL) all continued to show no concerning trends

Marked Reductions in CSF A β 42 and A β 40 at Month 2



Dose escalation in Phase 1 Part A **ongoing**

Multi-dose Part B
initiating in approved regions

Phase 2 CAA study initiation
planned for **early 2024**

Additional Value Creation Opportunities via Partnered Programs

FITUSIRAN

Hemophilia

Innovative approach to hemophilia A and B, with or without inhibitors

- Demonstrated reduction in annualized bleed rate across multiple Phase 3 studies
- NDA submission expected **2024**

sanofi

ELEBSIRAN (ALN-HBV02/VIR-2218)

Hepatitis B/D Virus Infection

Potential for functional cure of chronic HBV infection and chronic suppressive therapy for HDV infection

- Demonstrated robust reductions in HBsAg and potent antiviral activity in HDV
- Additional Phase 2 readouts expected in **2024**
- Alnylam opt-in right to elebsiran prior to Phase 3

VIR

CEMDISIRAN/POZELIMAB

Complement-Mediated Diseases

Unique siRNA/antibody combination providing potent C5 inhibition

- Demonstrated unprecedented LDH reduction in naïve patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)
- Phase 3 studies in Myasthenia Gravis and PNH **ongoing**
- Phase 3 in Geographic Atrophy **initiating in 1H24**

REGENERON

ALN-HSD and ALN-PNP

Nonalcoholic Steatohepatitis

Novel approach to NASH leveraging genetically validated targets

- Demonstrated improvement in biopsy-derived NAFLD Activity Score in NASH patients with ALN-HSD
- ALN-HSD Phase 2 and ALN-PNP Phase 1 studies **ongoing** in NASH patients

REGENERON

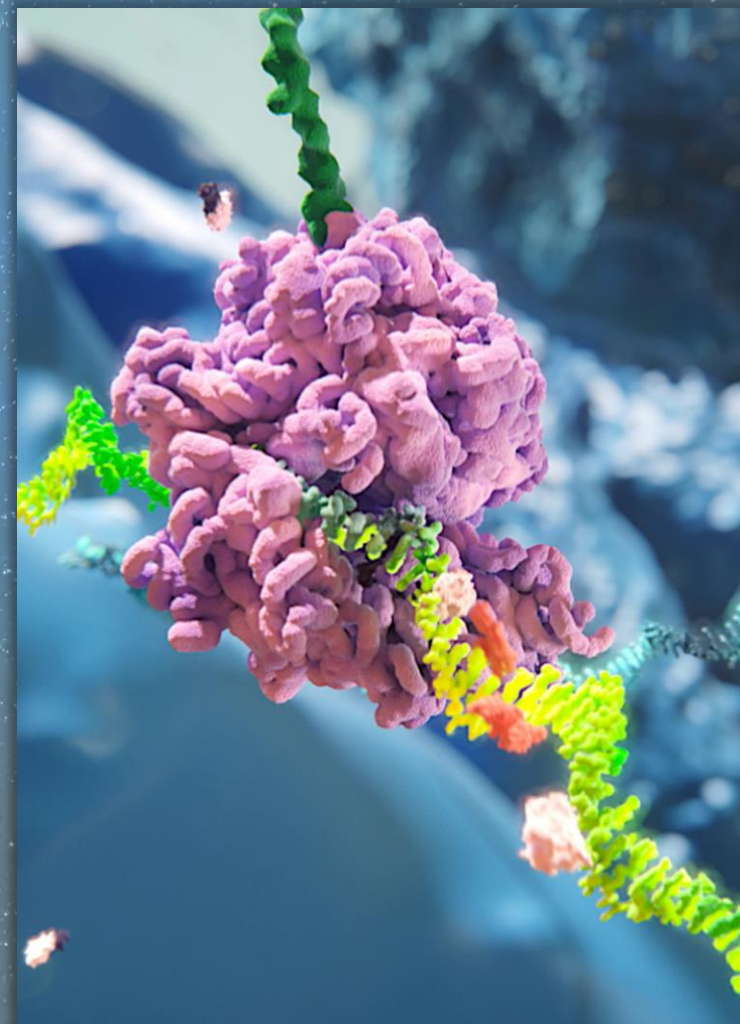


Chen
Living with hATTR Amyloidosis (Brazil)

**STRONG COMMERCIAL
GROWTH**

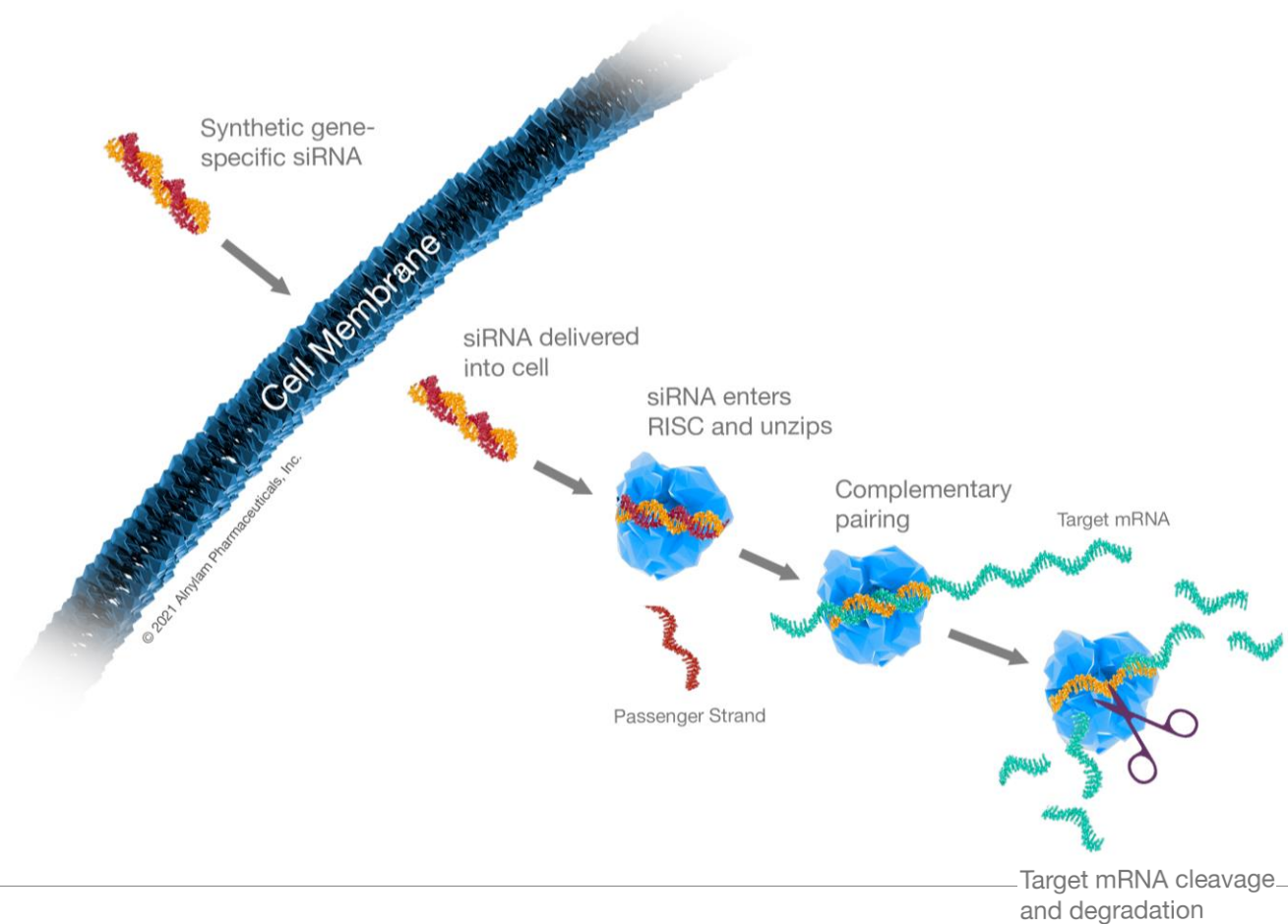


**ROBUST & HIGH-YIELD
R&D PIPELINE**



**SUSTAINABLE
INNOVATION ENGINE**

Organic Product Engine Capable of Sustaining Innovation for Future Growth

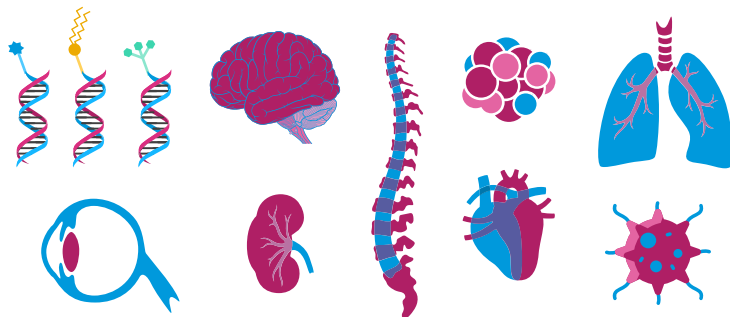


- Derisked platform with highly differentiated features:
 - ✓ Rapid knockdown
 - ✓ Clamped pharmacology
 - ✓ Extended durability
 - ✓ Favorable safety profile
- Modular and reproducible approach to drug development
- Historical probability of clinical success multiples higher than industry standards, driven by human genetics

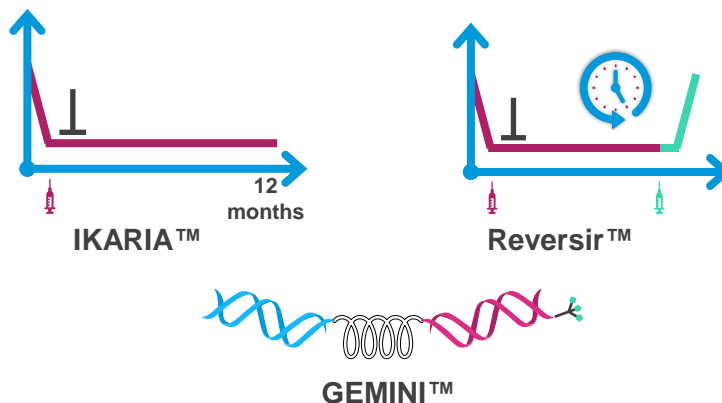
Multiple Sources of Sustainable Innovation Drive Robust Pipeline

Targeting Nine Alnylam-Led INDs Across Four Tissues by End of 2025

Extrahepatic Delivery



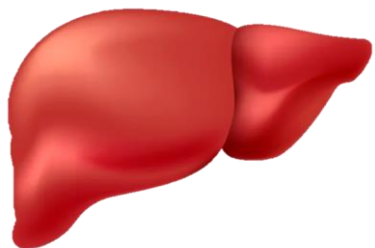
Platform Designs



Human Genetics

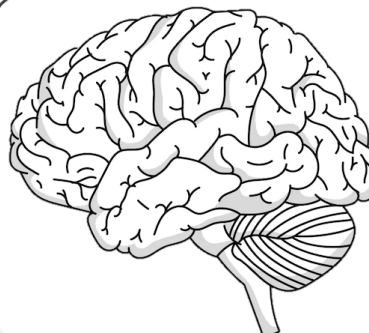


By End of 2025



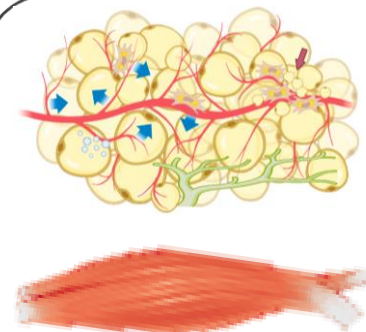
5 new liver
INDs

10+ including
partnered programs







2 new CNS
INDs

3+ including
partnered programs









2 new tissues
with INDs

Alnylam 2024 Goals

			Early	Mid	Late
   			Combined Net Product Revenue Guidance to be Provided at Q4/YE 2023 Earnings		
VUTRISIRAN	ATTR Amyloidosis	HELIOS-B Topline Results	●		
		sNDA Submission		●	
ALN-TTRsc04*	ATTR Amyloidosis	Initiate Phase 3 ATTR-CM Study			●
ZILEBESIRAN*	Hypertension	KARDIA-2 Phase 2 Topline Results	●		
		Initiate KARDIA-3 Phase 2 Study	●		
ALN-APP*	Alzheimer's Disease	Interim Phase 1 Part B Multi-Dose Results			●
		Initiate Phase 2 Study			●
	Cerebral Amyloid Angiopathy	Initiate Phase 2 Study	●		
ALN-KHK*	Type 2 Diabetes	Initiate Phase 1 Part B	●		
ALN-BCAT*	Hepatocellular Carcinoma	Initiate Phase 1 Study	●		
ADDITIONAL PROGRAMS		File 3 New INDs			●
KEY PARTNER-LED PROGRAM MILESTONES					
FITUSIRAN* (Sanofi)	Hemophilia	Submit NDA Filing	2024		
ELEBSIRAN* (Vir)	Chronic HBV/HDV Infection	Phase 2 Results	Q2, Q4		

* Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established.
Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4

Alnylam 2024 Goals

				Early	Mid	Late
<div><div><div></div><div></div><div></div><div></div></div><div>Combined Net Product Revenue Guidance to be Provided at Q4/YE 2023 Earnings</div></div>						●
VUTRISIRAN	<div><div><div>5 commercial products (4 wholly owned)</div><div> Phase 2 results</div><div> Phase 3 results</div><div>Vutrisiran sNDA filing (assuming positive study)</div></div><div><div>6 clinical study starts</div><div>3 new INDs</div></div></div>	●				
ALN-TTRsc04*			●			
ZILEBESIRAN*						
ALN-APP*			●			
ALN-KHK*			●			
ALN-BCAT*						
ADDITIONAL			●			
KEY PARTNER-LED PROGRAM MILESTONES						
FITUSIRAN* (Sanofi)	Hemophilia	Submit NDA Filing	2024			
ELEBSIRAN* (Vir)	Chronic HBV/HDV Infection	Phase 2 Results	Q2, Q4			

* Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established.
Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4

Ambitious Five-Year Strategy to Drive Growth



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: $\geq 40\%$ revenue CAGR through YE 2025

Profitability: Achieve sustainable non-GAAP profitability within period

| | Thank You!