

Nathan (USA)
Diagnosed with AHP

Alylam Pharmaceuticals

January 2023

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 leading 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: 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 January 2022 leadership transition on our ability to attract and retain talent and to successfully execute on our "Alnylam P5x25" strategy; the finalization and audit of our fourth quarter and 2022 fiscal year financial results, which could potentially result in changes or adjustments to the selected preliminary financial results presented herein; 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; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, 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 or 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 a current government investigation 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. In addition, any forward-looking statements represent our views only as of the date of this presentation and should not be relied upon as representing our views as of any subsequent date. We explicitly disclaim any obligation, except to the extent required by law, to update such statements.

This presentation references non-GAAP financial measures. These measures are not in accordance with, or an alternative to, GAAP, and may be different from non-GAAP financial measures used by other companies. Percentage changes in revenue growth at Constant Exchange Rates, or CER, are non-GAAP financial measures which are presented excluding the impact of changes in foreign currency exchange rates for investors to understand the underlying business performance. CER represents growth calculated as if the exchange rates had remained unchanged from those used during 2021.

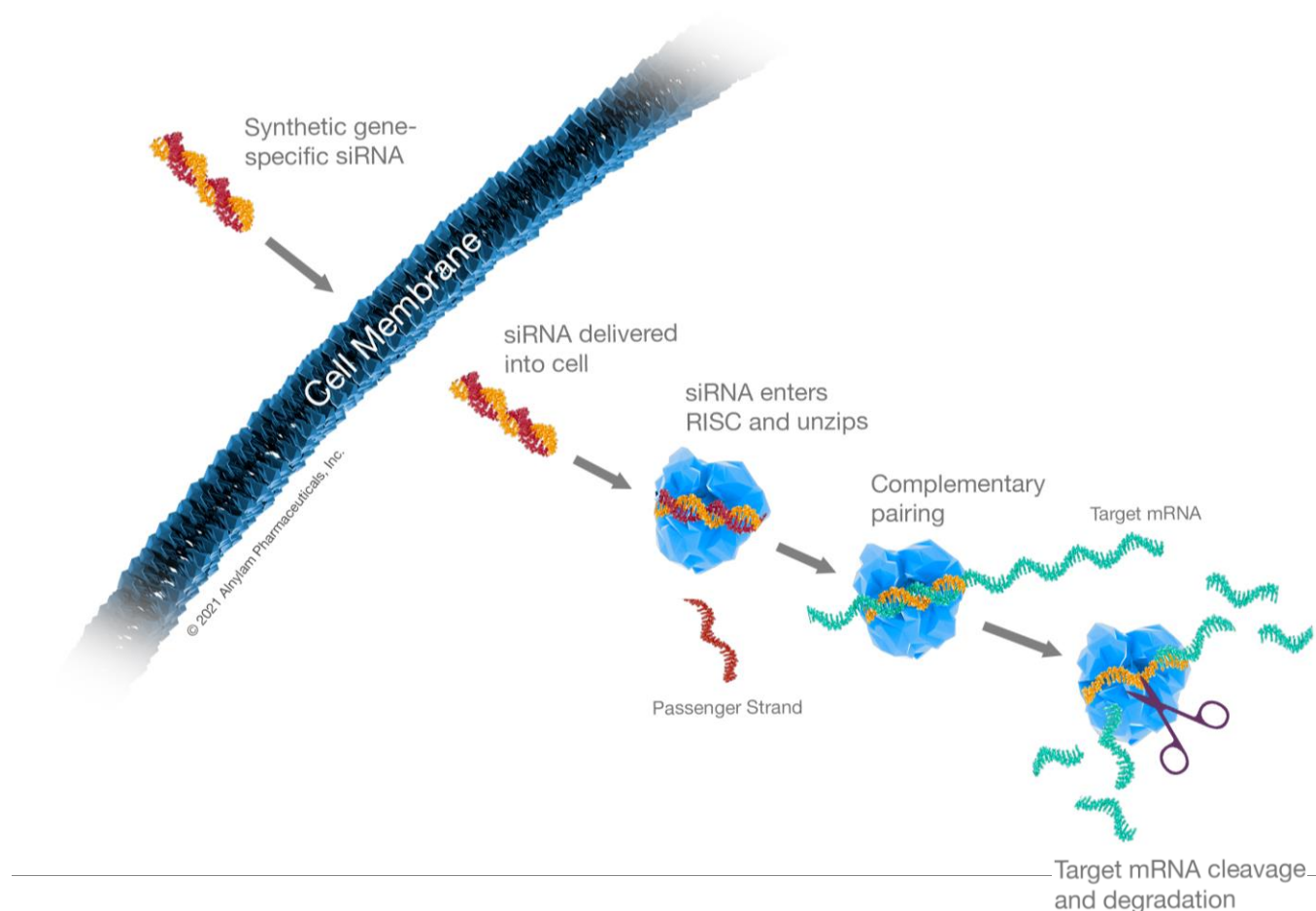
Alnylam Poised to Become a Top-Tier Biotech

Pioneer in RNAi Therapeutics

- 5 medicines approved in < 4 years
- Robust clinical pipeline across rare, specialty, and prevalent diseases
- Global footprint with strong commercial capabilities
- Strong balance sheet, on path toward financial self-sustainability

Highly differentiated with proven track record and derisked platform

- Modular and reproducible approach to drug development
- Historic probability of clinical success multiples higher than industry standards
- Organic product engine capable of sustaining innovation for future growth
- Track record of setting and exceeding 5-year goals



Notable Accomplishments in 2022



Combined net product revenues of
\$894 million*
 (35% growth YoY)

APOLLO-B

Reported positive Phase 3 study results in
 patients with ATTR-CM;
sNDA submitted Dec. 8, 2022



FIFTH
 RNAi therapeutic approved



CTA filings

- ALN-TTRsc04
- ALN-KHK
- ALN-PNP



Continued recognition of
award winning culture



Initiated first-in-human
 clinical study of an RNAi
 therapeutic in CNS
(ALN-APP)



Maintained strong financial position

- **\$2.2 billion in cash**
at year-end 2022*
- Lowered cost of capital via
\$1,035 million convertible
 financing

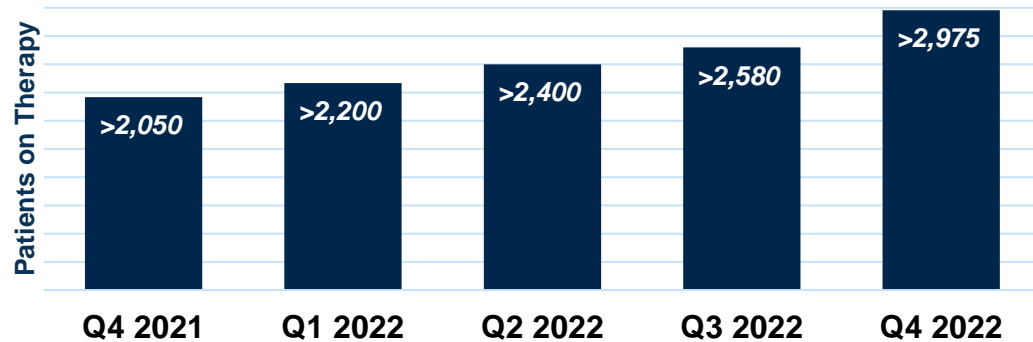


Label expansion

- **OXLUMO** for
 advanced PH1

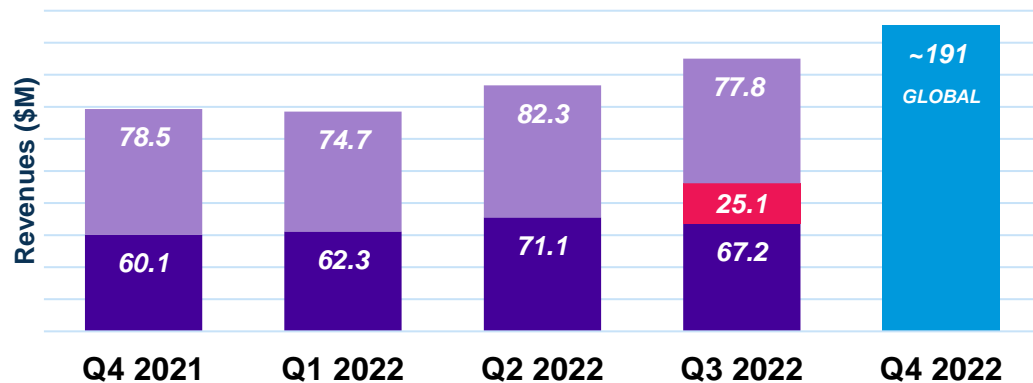
Robust Commercial Execution Driven by Strong AMVUTTRA Launch

2022 Combined Net Product Revenues (\$894M) Represent 35% YoY Growth (43% CER)*

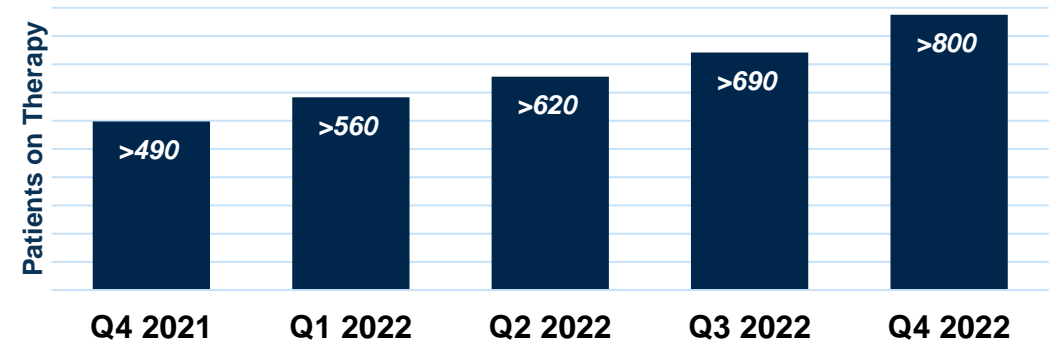
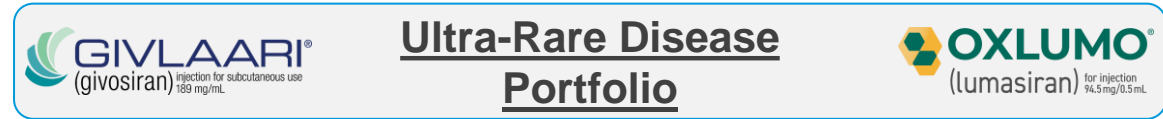


~\$651M
2022 revenues

>2,975 patients
as of December 31, 2022

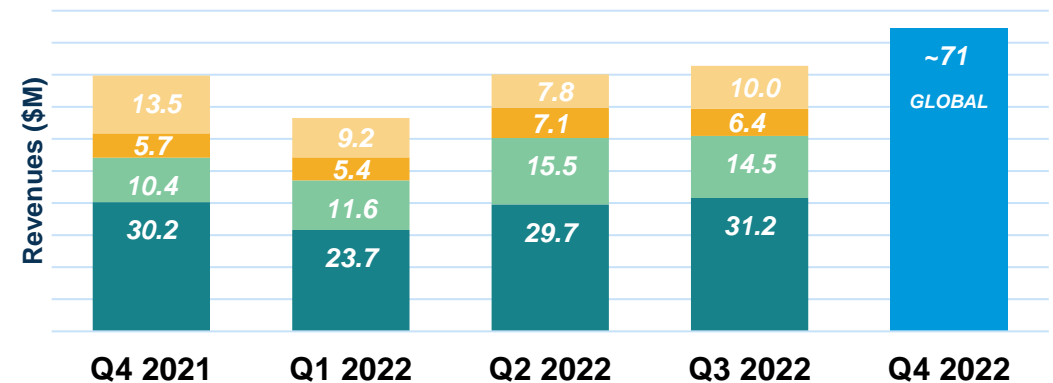


U.S. ONPATTRO ROW ONPATTRO U.S. AMVUTTRA ROW AMVUTTRA



~\$243M
2022 revenues

>800 patients
as of December 31, 2022








U.S. GIVLAARI ROW GIVLAARI U.S. OXLUMO ROW OXLUMO

* 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 2023. CER = Constant Exchange Rate, representing growth calculated as if the exchange rates had remained unchanged from those used during 2021. CER is a non-GAAP financial measure. A reconciliation of this non-GAAP financial measure to the comparable GAAP measure is available in our press release dated January 8, 2023, which is available in the Investors section of our website at www.alnylam.com.

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

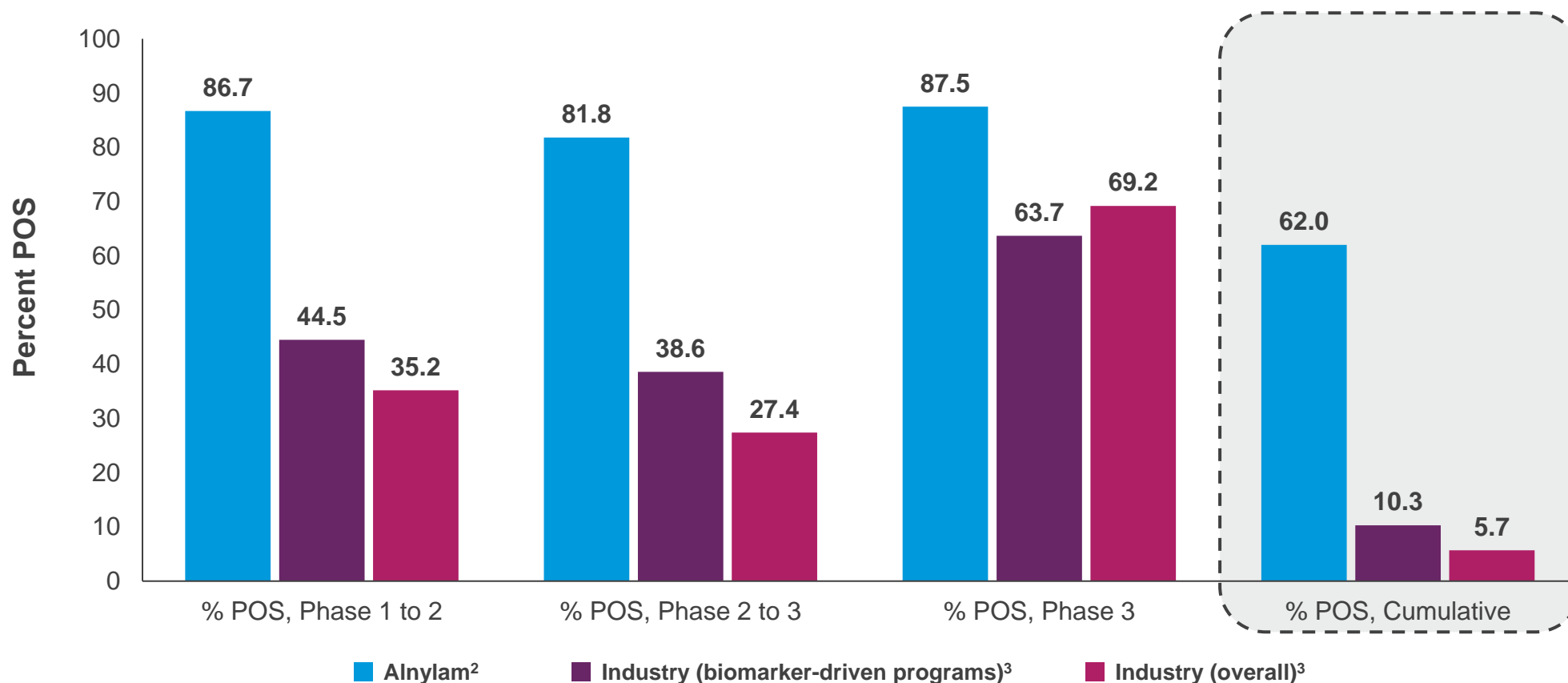
		EARLY/MID-STAGE (IND/CTA Filed-Phase 2)	LATE STAGE (Phase 2-Phase 3)	REGISTRATION/ COMMERCIAL ¹	COMMERCIAL RIGHTS
 onpattro (patisirán)	<i>hATTR Amyloidosis with PN</i>			●	Global
 amvuttra (vutrisiran)	<i>hATTR Amyloidosis with PN</i>			●	Global
 GIVLAARI (givosiran)	<i>Acute Hepatic Porphyria</i>			●	Global
 OXLUMO (lumasiran)	<i>Primary Hyperoxaluria Type 1</i>			●	Global
 LEQVIO (incisiran)	<i>Hypercholesterolemia</i>			●	Milestones & up to 20% Royalties ²
Patisiran**	<i>ATTR Amyloidosis with CM</i>			●	Global
Vutrisiran	<i>ATTR Amyloidosis with CM</i>		●		Global
Fitusiran*	<i>Hemophilia</i>		●		15-30% Royalties
Cemdisiran (+/- Pozelimab)^{3*}	<i>Complement-Mediated Diseases</i>		●		Global; Milestone/Royalty
ALN-TTRsc04*	<i>ATTR Amyloidosis</i>	●			Global
Belcesiran^{4*}	<i>Alpha-1 Liver Disease</i>	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)^{5*}	<i>Hepatitis B Virus Infection</i>	●			50-50 option post-Phase 2
Zilebesiran*	<i>Hypertension</i>	●			Global
ALN-HSD^{6*}	<i>NASH</i>	●			Royalty
ALN-APP*	<i>Alzheimer's Disease; Cerebral Amyloid Angiopathy</i>	●			50-50
ALN-PNP*	<i>NASH</i>	●			50-50
ALN-KHK*	<i>Type 2 Diabetes</i>	●			Global

¹ Includes marketing application submissions; ² Novartis has obtained global rights to develop, manufacture and commercialize incisiran; 50% of incisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; ³ Alnylam and Regeneron are evaluating potential combinations of the investigational therapeutics cemdisiran and pozelimab; ⁴ Dicerna is leading and funding development of belcesiran; ⁵ Vir is leading and funding development of ALN-HBV02; ⁶ Regeneron is leading and funding development of ALN-HSD; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established; ** U.S. sNDA has been filed. **As of January 2023**

High-Yield Productivity of Alnylam RNAi Therapeutics Platform

Comparison of Historical Metrics to Alnylam Portfolio over Past Decade¹

Probability of Success (POS) by Phase Transition



¹ Analysis of Alnylam programs from January 2012 through December 2022; Past rates of Alnylam and industry respectively may not be predictive of the future

² Alnylam programs biomarker-driven at all stages of development (100%); figures include Alnylam-originated molecules now being developed by partners

³ Wong et al., Biostatistics (2019) 20, 2, pp. 273–286

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: ≥40% revenue CAGR through YE 2025

Profitability: Achieve sustainable non-GAAP profitability within period

Multiple Drivers of Future Growth

TTR Franchise Leadership

Expansion Beyond Rare Diseases

Engine for Sustainable Innovation



Multiple Drivers of Future Growth

TTR Franchise Leadership

Expansion Beyond Rare Diseases

Engine for Sustainable Innovation



Liana (Brazil)
Diagnosed with
hATTR amyloidosis



ATTR Amyloidosis

Rare, Progressively Debilitating, and Fatal Disease

Description

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

Hereditary ATTR (hATTR) Amyloidosis

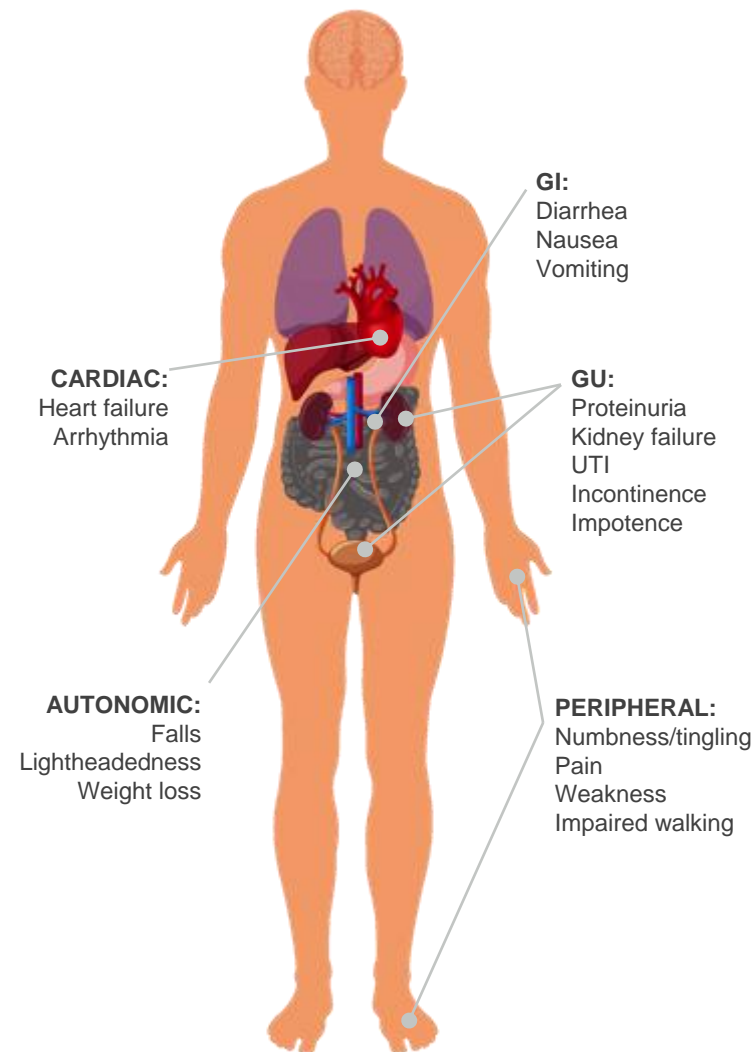
~50,000

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

Building a Leading TTR Franchise

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

onpattro
(patisirán)
lipid complex injection
10 mg/0.5 mL

APOLLO

*hATTR Amyloidosis with PN & Mixed**

2018 – 2022

Patisiran

APOLLO·B

ATTR Amyloidosis with CM (incl. WT)‡

Vutrisiran

**Biannual Dosing
Regimen**

hATTR Amyloidosis with PN & Mixed†

amvuttra
(vutrisiran)
injection
25 mg/0.5 mL

HELIOS·A

hATTR Amyloidosis with PN & Mixed†

onpattro
(patisirán)
lipid complex injection
10 mg/0.5 mL

APOLLO

*hATTR Amyloidosis with PN & Mixed**

2022 – 2024

Novel siRNA Conjugates[^]

Ocular & CNS hATTR Amyloidosis

ALN-TTRsc04

ATTR Amyloidosis

TBD¹

Phase 3

Stargardt Disease

Vutrisiran

HELIOS·B

ATTR Amyloidosis with CM (incl. WT)‡

Patisiran

APOLLO·B

ATTR Amyloidosis with CM (incl. WT)‡

amvuttra
(vutrisiran)
injection
25 mg/0.5 mL

HELIOS·A

hATTR Amyloidosis with PN & Mixed†

onpattro
(patisirán)
lipid complex injection
10 mg/0.5 mL

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 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

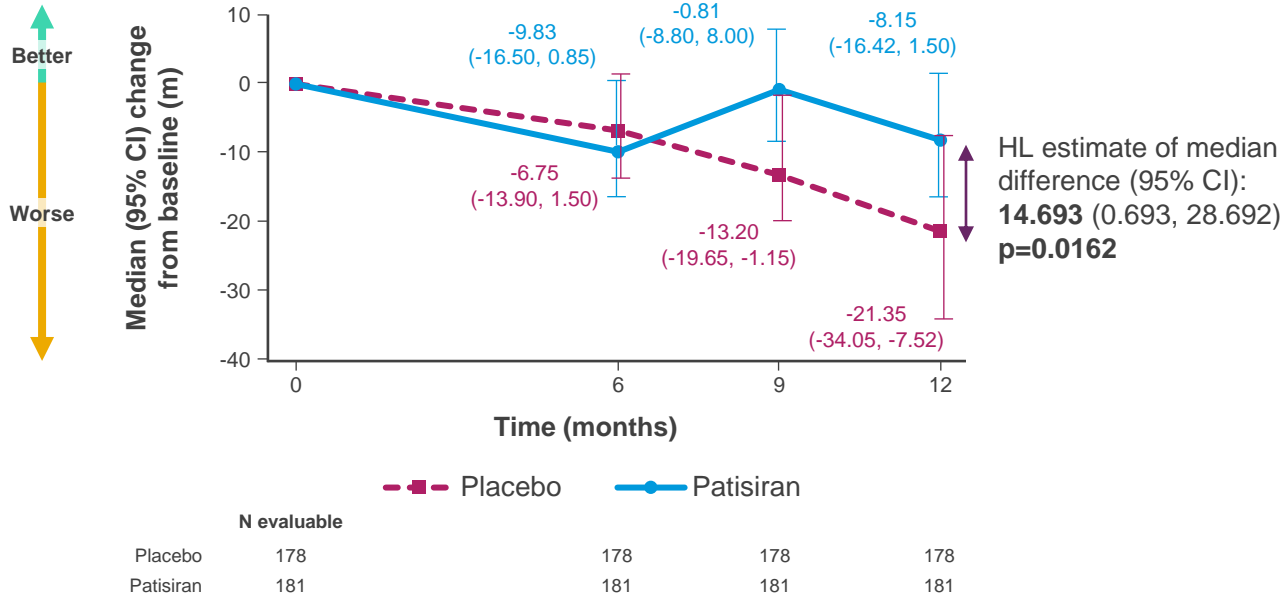
† AMVUTTRA is approved in the U.S. for the treatment of the PN of hATTR amyloidosis in adults and in the EU and Japan for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy; ^ Novel siRNA conjugate development candidates for ocular or CNS hATTR amyloidosis not yet selected; ¹ The Company is considering options for the best path forward to bring an RNAi therapeutic to patients with Stargardt Disease.

Patisiran sNDA Submitted with Positive **APOLLO-B** Study Results

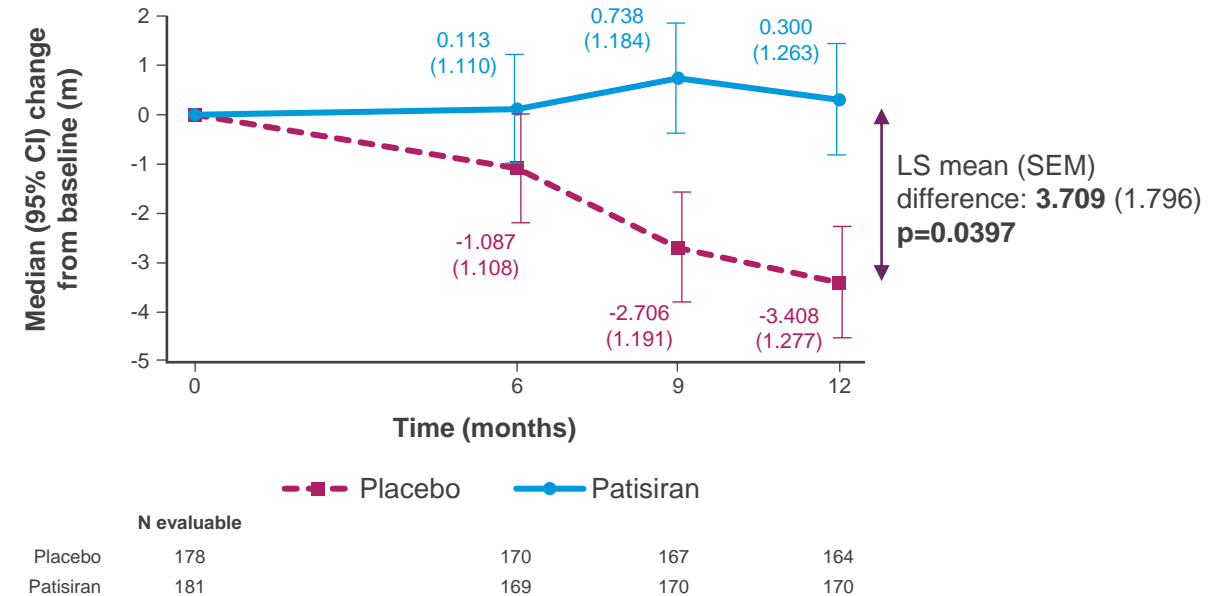
If Approved, Broadens Commercial Opportunity to Full Spectrum of ATTR Amyloidosis Patients

Patisiran demonstrated statistically significant and clinically meaningful improvements in functional capacity, health status and quality of life compared to placebo at month 12

Change from Baseline in 6-MWT^a



Change From Baseline in KCCQ-OS using MMRM^b



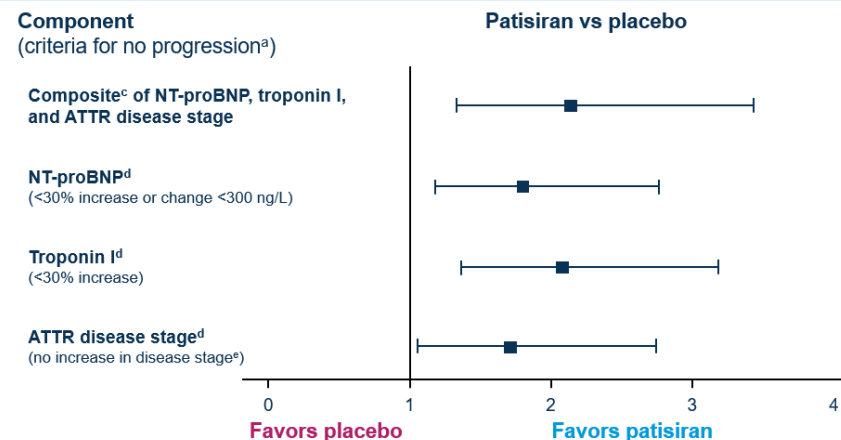
^a Primary endpoint analysis based on the stratified Wilcoxon Rank Sum test. Median (95% CI) change from baseline values were based on the observed 6-MWT data and the imputed values; for each patient, the change from baseline was averaged across 100 complete datasets. Missing Month 12 values due to non-COVID-19 death or inability to walk due to progression of ATTR amyloidosis were imputed as the worst 10th percentile change observed across all patients in the double-blind period, capped by the worst possible change for the patient (i.e., 0 minus the patient's baseline 6-MWT). Missing Month 12 data due to other reasons were multiply imputed (assuming data were missing at random) to create 100 complete datasets. At baseline, the median (range) 6-MWT was 358.000 (155.70, 808.00) in the patisiran group and 367.740 (130.00, 740.00) in the placebo group. Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; HL, Hodges-Lehmann; m, meters. ^b MMRM model. Missing data not explicitly imputed and assumed to be missing at random. At baseline, the mean (±SD) KCCQ-OS was 69.836 (21.178) in the patisiran group and 70.330 (20.709) in the placebo group. Abbreviations: KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; LS, least squared; MMRM, mixed model repeated measures; SD, standard deviation; SEM, standard error of mean.

Safety and Exploratory Endpoints Support Patisiran's Therapeutic Potential

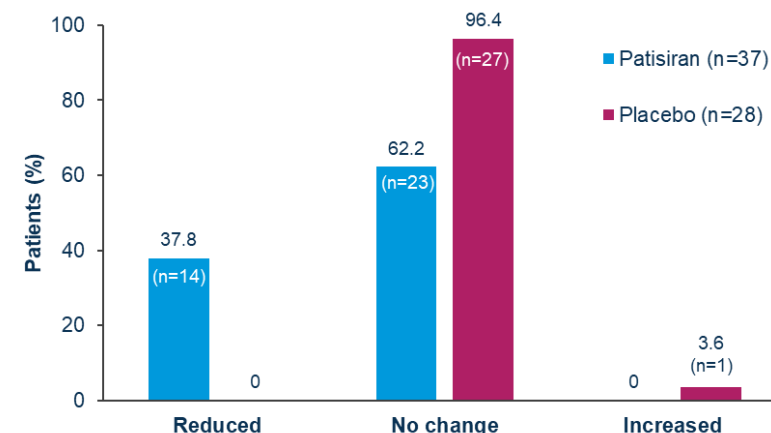
APOLLO-B

- Majority of AEs were mild or moderate in severity
- AEs $\geq 5\%$ in the patisiran group observed 3% more commonly than in placebo included infusion-related reaction (12.2% vs 9.0%), arthralgia (7.7% vs 4.5%), and muscle spasms (6.6% vs 2.2%)
- Compared with placebo, patisiran demonstrated fewer events within Standardized MedDRA Queries (SMQs) exploring potential cardiac safety issues

Biomarker Based Disease Progression at Month 12^{a,b}



Change from Baseline in Perugini Grade at Month 12^c



^a Garcia-Pavia P, et al. Eur J Heart Fail. 2021 Jun;23(6):895–905; ^b Patients who are missing Month 12 due to COVID-19 are excluded from analysis. Odds ratio and 95% CI from Cochran–Mantel–Haenszel test stratified by baseline tafamidis use; ^c For the composite parameter, the summary presents the odds ratio (95% CI) of no progression on any component (ie, $<30\%$ increase or change <300 ng/L in NT-proBNP AND $<30\%$ increase in troponin I AND no increase in ATTR disease stage); ^d For each component, the summary presents the odds ratio (95% CI) of no progression on the specified component (ie, $<30\%$ increase or change <300 ng/L for NT-proBNP, $<30\%$ increase for troponin I, and no increase for ATTR disease stage); ^e Gillmore JD, et al. Eur Heart J. 2018 Aug;39(30):2799–2806; ^f Analysis includes patients in the patisiran (n=37) and placebo (n=28) arms from the full analysis set with evaluable data at baseline and Month 12. 40 patients in the patisiran group and 37 patients in the placebo group were evaluated at baseline. 37 patients in the patisiran group and 28 patients in the placebo group were evaluated at Month 12.

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 & recurrent all-cause hospitalizations & urgent HF visits
- 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**

Significant Commercial Potential in ATTR Amyloidosis*

Initial Entry with Patisiran and Potential Expansion with Vutrisiran

APOLLO



- Established RNAi therapeutics in hATTR amyloidosis with PN
- Reversal in neuropathy impairment

**Strong Foundation
with Patisiran**

HELIOS·A



- Demonstrated efficacy and safety in hATTR amyloidosis with PN
- Subcutaneous administration with infrequent dosing

**Continued Growth
in hATTR with PN
with Vutrisiran**

APOLLO·B



- First RNAi therapeutic demonstrating impact across a spectrum of disease manifestations in ATTR amyloidosis with CM
- Encouraging clinical efficacy and safety

**Rapid Path to Larger
Patient Population
with Patisiran**

HELIOS·B



- Potential for a robust efficacy profile, including outcomes data
- Potential best-in-class product profile

**Transformative
Potential with
Vutrisiran**

Multiple Drivers of Future Growth

TTR Franchise Leadership

Expansion Beyond Rare Diseases

Engine for Sustainable Innovation



RNAi Therapeutics Profile Supports Potential Beyond Rare Diseases



- Durability
- Clamped pharmacology
- Potential for improved adherence
- Supportive safety profile



ULTRA RARE

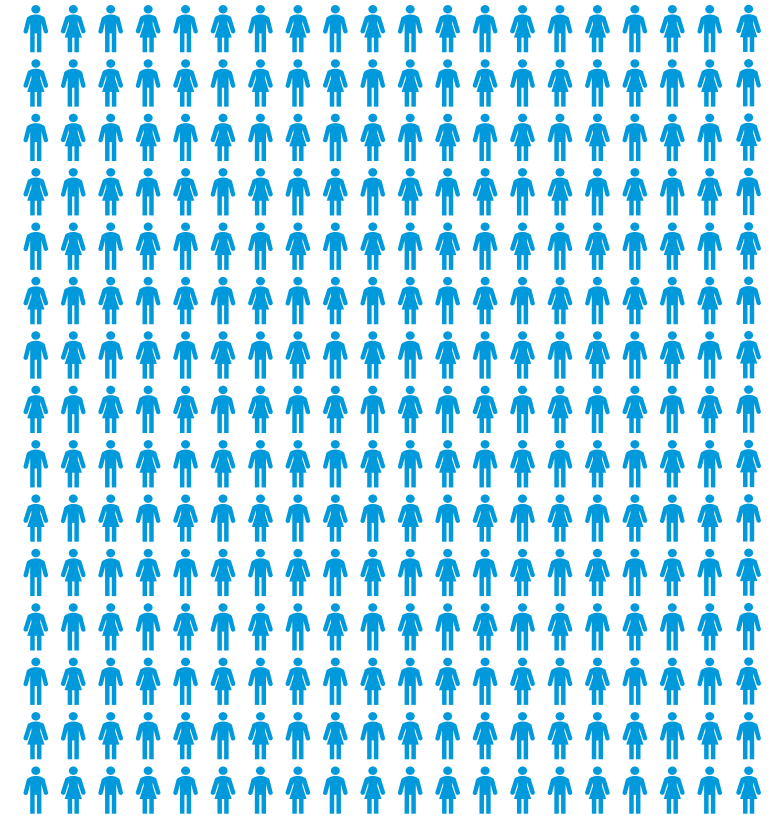
GIVLAARI®
OXLUMO®



RARE/SPECIALTY

ONPATTRO®: hATTR w/ PN¹
AMVUTTRA®: hATTR w/ PN²
Patisiran: ATTR w/ CM³
Vutrisiran: ATTR w/CM³

ALN-TTRsc04
Fitusiran
Belcesiran



PREVALENT

Leqvio®⁴
Zilebesiran
ALN-HBV02 (VIR-2218)
ALN-APP

ALN-HSD
ALN-PNP
ALN-KHK

1 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; 2 AMVUTTRA is approved in the U.S. for the treatment of the PN of hATTR amyloidosis in adults and in the EU and Japan for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy; 3 Patisiran and vutrisiran 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 their safety or effectiveness in this population; 4 Leqvio is approved in the U.S. for the treatment of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) and in the EU for the treatment of hypercholesterolemia or mixed dyslipidemia.

Uncontrolled Hypertension is a Global Health Crisis

Hypertension is Highly Prevalent and Carries Substantial Risk of CV Morbidity and Mortality

Primary Hypertension¹
in 7 Major Markets, 2020

~219MM

High CV Risk with Hypertension²
in 7 Major Markets, 2020³

~77MM

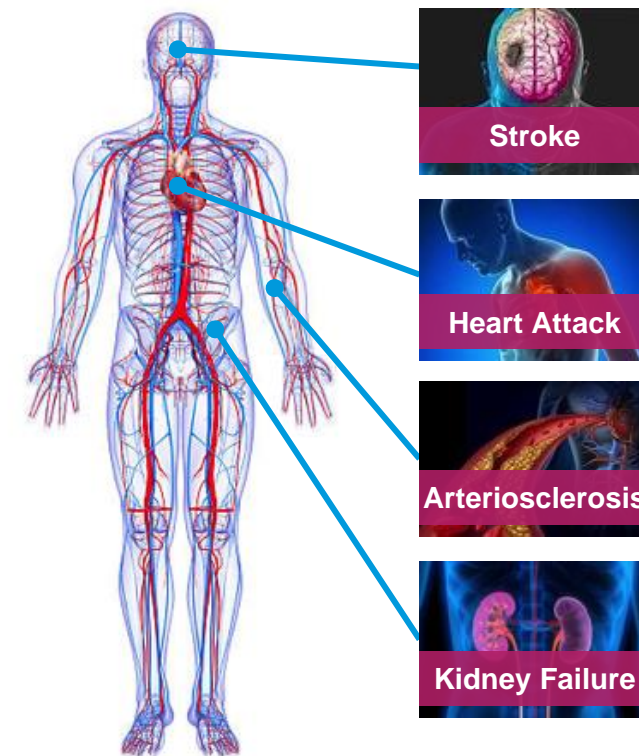
~70%

UNCONTROLLED HYPERTENSION
(>130/80 mmHg despite treatment)⁴

Hypertension risk further exacerbated by **variability in BP control**,
lack of nighttime dipping, and **poor medication adherence**

Together, contribute to substantial risk of CV morbidity and mortality

Potential complications of
uncontrolled hypertension



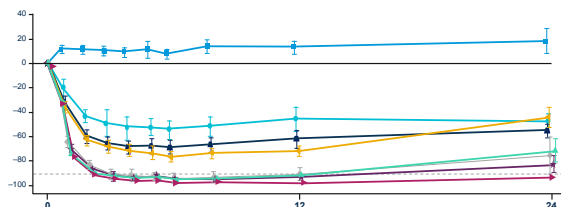
BP, blood pressure; CV, cardiovascular; MM, million; mmHg, millimeters of mercury

1. Extrapolated for 7 major markets (7MM) based on proportion of US hypertension population with prior history of CVD or Framingham Risk Score of >10%, excluding patients with history of stroke and women of child-bearing potential; 2. Estimated from multiple sources and internal estimates: Dorans et al. J Am Heart Assoc 2018;7:e008888; Al Kibria et al. Hypertens Res. 2019;42:1631-43; CDC Hypertension Cascade. 2019; High CV risk: ASCVD risk score ≥20% and/or history of CVD; 3. Excluding stroke and WOCBP; 4. U.S. Department of Health and Human Services. The Surgeon General's Call to Action to Control Hypertension. Washington, DC: U.S. Department of Health and Human Services, Office of the Surgeon General, 2020.

Zilebesiran: Potential Novel Treatment for Patients with Hypertension

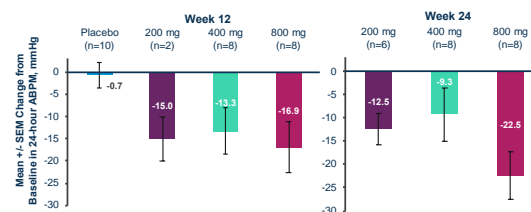
Compelling Phase 1 Data Support Transformative Product Profile

Serum AGT Lowering



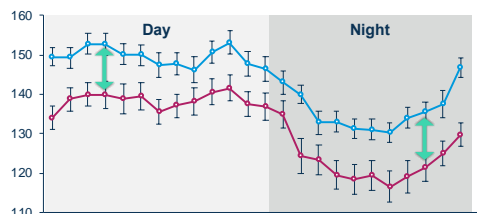
>90% mean serum AGT reduction for 6 months*

Blood Pressure Reduction



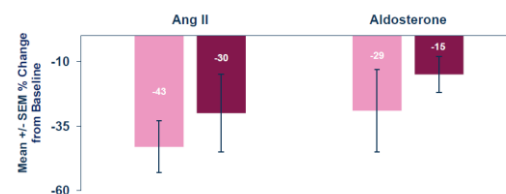
>20 mmHg SBP reduction at 6 months*

Consistent BP Reduction



Tonic BP control demonstrated over 24hr*

Change in RAAS Biomarkers



Durable reduction in Ang II & aldosterone*

KARDIA₁

Monotherapy Phase 2 Study (N = 394)

- Exploring multiple doses and dosing regimens
- Enrollment completed **December 2022**
- Topline results expected **mid-2023**

KARDIA₂

Combination Phase 2 Study (N ~ 630)

- Background treatment standardized with ARB, calcium channel blocker or diuretic
- Enrollment completion expected **early 2023**
- Topline results expected **at or around year-end 2023**

Additional Growth Opportunities via Partnered Programs

ALN-HBV02 (VIR-2218)

Hepatitis B/D Virus Infection

*Potential for functional cure
of chronic HBV infection*

Additional Phase 2 HBV readouts
expected in **2023**

Phase 2 HDV study ongoing;
data expected in **2023**

Alnylam opt-in right to VIR-2218
prior to Phase 3

VIR

FITUSIRAN

Hemophilia

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

Demonstrated reduction in annualized
bleeding rate

Additional Phase 3 data with lower
doses expected **late 2023**

NDA submission expected **2024**

sanofi

CEMDISIRAN/POZELIMAB

Complement-Mediated Diseases

*Novel approach providing
potent C5 inhibition*

Phase 3 Myasthenia Gravis
study **ongoing**

Phase 2 and 3 Paroxysmal Nocturnal
Hemoglobinuria studies **ongoing**

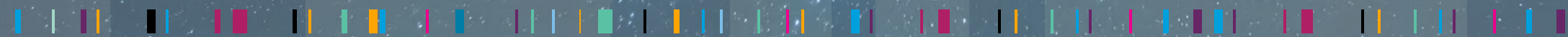
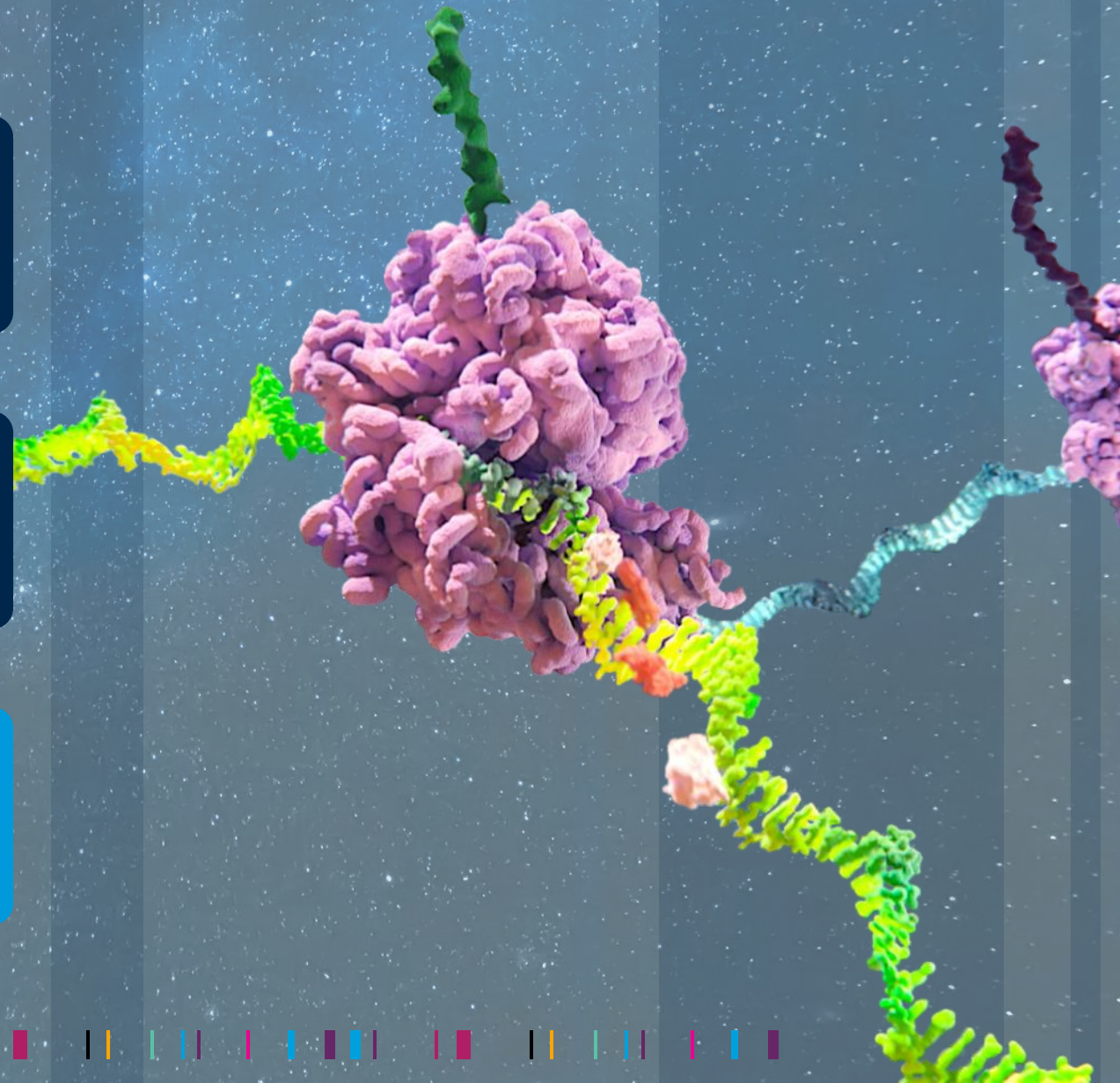
REGENERON

Multiple Drivers of Future Growth

TTR Franchise Leadership

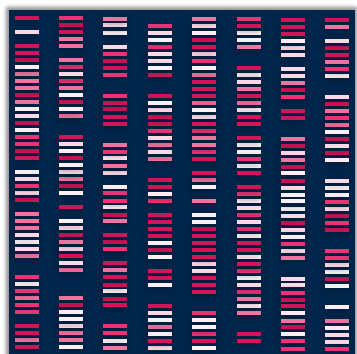
Expansion Beyond Rare Diseases

Engine for Sustainable Innovation



Two-Decade Track Record of Industry Leadership in RNAi

Human Genetics

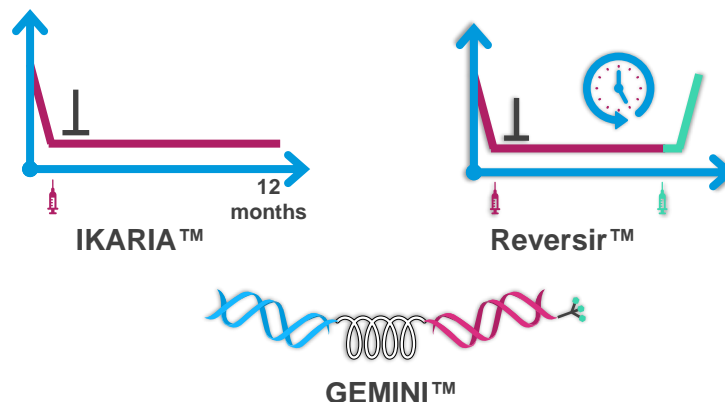


+
Our
Future
Health

biobank^{uk}

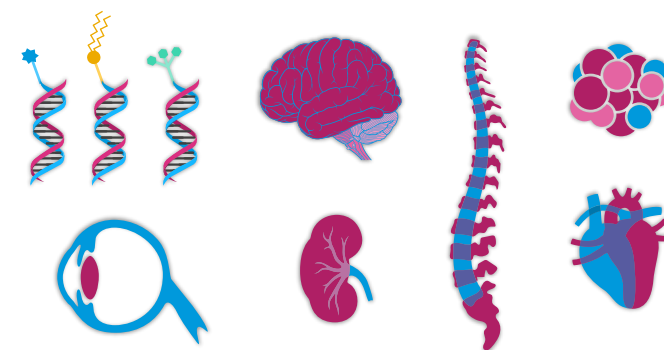
- Sourcing novel, genetically validated targets
- Secured access to large PheWAS databases
- Proven ability to uncover novel gene targets

Platform Designs



- IKARIA™ enables robust target knockdown with annual dosing potential
- Reversir™ provides tailored control of RNAi pharmacology
- GEMINI™ combines siRNAs for simultaneous silencing of two transcripts

Extrahepatic Delivery



- Novel conjugates with variety of ligands for delivery beyond liver
- C16 conjugate provides robust target knockdown with wide biodistribution and long duration of action in CNS
- Peptide and antibody-based approaches being explored for targeted siRNA delivery to new tissues

Expanding Beyond Liver with First CNS Program in Clinic

Multiple Patient Populations with High Unmet Need

ALN-APP lowers APP production *at its source*,
upstream of pathogenic process

Alzheimer's Disease (AD)

- Over 5M people affected by AD in U.S. (30M+ WW)
- Current therapies not shown to halt disease progression
- ALN-APP could reduce both intracellular and extracellular drivers of disease pathology

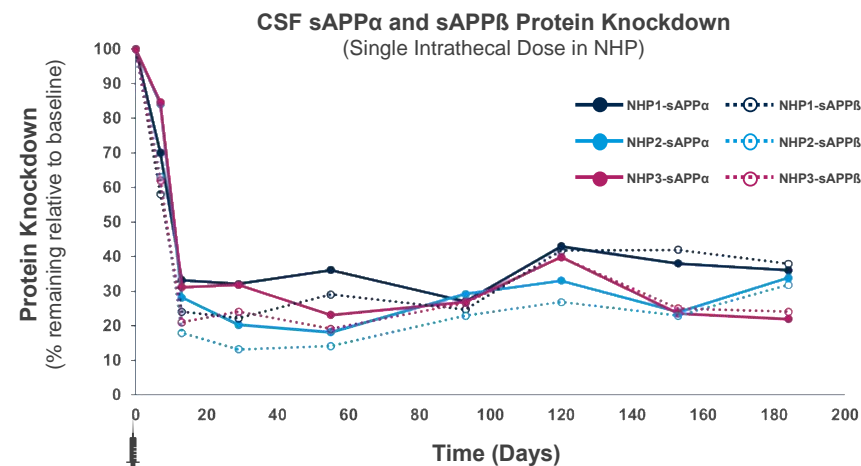
Cerebral Amyloid Angiopathy (CAA)

- Second-leading cause of ICH after hypertension
- No specific treatments available for CAA
- ALN-APP could lower all A β isoforms including A β 40, primary component of vascular amyloid deposits

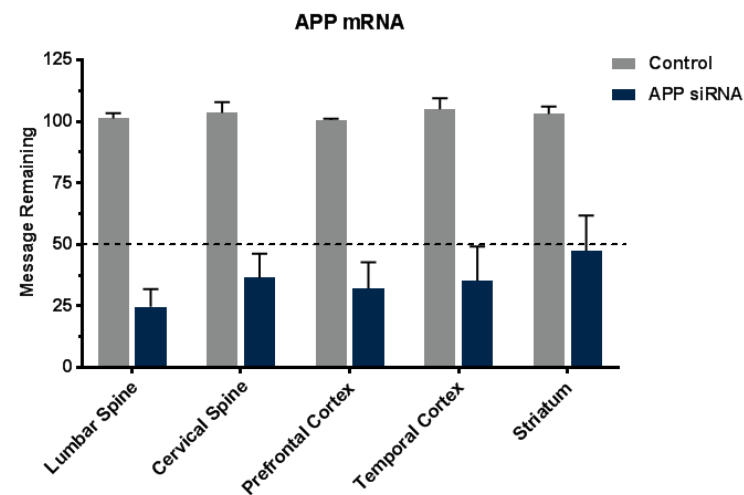
Dose escalation in Part A **ongoing**

Topline Phase 1 data expected **early 2023**

Durable Effect in NHP



Broad Distribution in NHP







Alnylam 2023 Goals

			Early	Mid	Late
<div><div></div><div></div><div></div><div></div></div>		Combined Net Product Revenue Guidance to be Provided at Q4/YE 2022 Earnings			●
PATISIRAN	ATTR Amyloidosis	FDA Approval of sNDA			●
VUTRISIRAN	ATTR Amyloidosis	Biannual Dosing Regimen Data	●		
		Submit sNDA for Biannual Dosing Regimen	●		
ALN-TTRsc04*	ATTR Amyloidosis	Phase 1 Topline Results			●
ZILEBESIRAN*	Hypertension	Complete KARDIA-2 Enrollment	●		
		KARDIA-1 Phase 2 Topline Results		●	
		KARDIA-2 Phase 2 Topline Results (at or around year-end)			●
ALN-APP*	Alzheimer’s Disease	Phase 1 Topline Results	●		
ALN-KHK*	Type 2 Diabetes	Initiate Phase 1 Study	●		
		Phase 1 Topline Results			●
ADDITIONAL PROGRAMS		File 2-4 New INDs			●
PARTNERED PROGRAM MILESTONES					
FITUSIRAN* (Sanofi)	Hemophilia	ATLAS Phase 3 Topline Results			●
ALN-HBV02* (Vir)	Chronic HBV/HDV Infection	Phase 2 Results	●		●
ALN-PNP* (Regeneron)	NASH	Initiate Phase 1 Study	●		

* 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 2023 Goals

			Early	Mid	Late
   					●
Combined Net Product Revenue Guidance to be Provided at Q4/YE 2022 Earnings					
PATISIRAN	ATTR Amyloidosis	FDA Approval of sNDA			●
VUTRISIRAN					
ALN-TTRsc04*					●
ZILEBESIRAN*			●		●
ALN-APP*					
ALN-KHK*					●
ADDITIONAL					●
PARTNERED PROGRAM MILESTONES					
FITUSIRAN* (Sanofi)	Hemophilia	ATLAS Phase 3 Topline Results			●
ALN-HBV02* (Vir)	Chronic HBV/HDV Infection	Phase 2 Results	●		●
ALN-PNP* (Regeneron)	NASH	Initiate Phase 1 Study	●		

- Commercial execution across four products
- Ten clinical readouts from proprietary and partner-led programs
- Potential label expansion for ONPATTRO in ATTR amyloidosis with cardiomyopathy
- First human data for RNAi therapeutic in CNS
- 2-4 new INDs

* 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

Nurturing a Winning Culture

Commitment to People



Scientific Innovation



Patisiran, an RNAi Therapeutic,
for Hereditary Transthyretin Amyloidosis

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lumasiran, an RNAi Therapeutic for Primary
Hyperoxaluria Type 1



Phase 3 Trial of RNAi Therapeutic Givosiran for Acute
Intermittent Porphyria

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

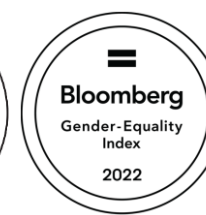
A Highly Durable RNAi Therapeutic
Inhibitor of PCSK9

OTS Paper of the Year 2022



Expanding RNAi therapeutics
to extrahepatic tissues with
lipophilic conjugates
Brown, et al.

Diversity, Equity, & Inclusion



Social Responsibility



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| || **Thank You!**