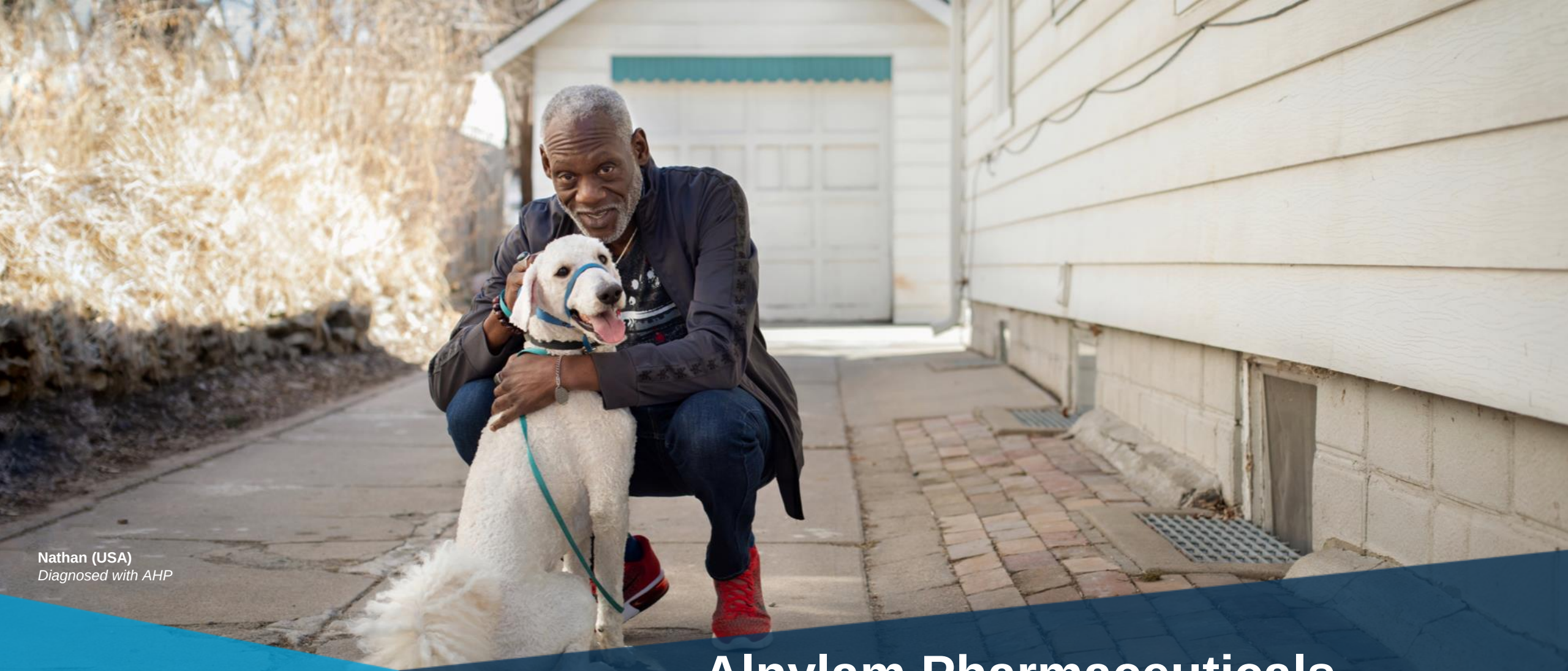


Nathan (USA)
Diagnosed with AHP

Alnylam Pharmaceuticals

September 2022

Alnylam®@20

Alnylam Forward Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, including but not limited to expectations regarding our aspiration to become a leading biotech company and the planned achievement of our "*Alnylam P^{5}x25*" strategy, our ability to attain financial self-sustainability, the drivers of our future growth potential, including the potential of our TTR franchise and the launch of AMVUTTRA for the treatment of hATTR amyloidosis patients with polyneuropathy in the U.S. and, if approved by other regulatory authorities in additional territories, the safety and efficacy of patisiran for the treatment of ATTR amyloidosis with cardiomyopathy, the expected timing of the presentation of additional data from the APOLLO-B study, the expected timing of an sNDA filing for patisiran, the evaluation of vutrisiran in the HELIOS-B Phase 3 study for the treatment of patients with ATTR amyloidosis with cardiomyopathy and the expected timing for topline data from that study, the potential opportunity for RNAi therapeutics in prevalent diseases, and the potential of our engine for sustainable innovation including the potential for improved product profiles to emerge from our IKARIA and GEMINI platforms, as well as the achievement of additional pipeline and regulatory milestones during 2022 and beyond with value creation potential. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; the potential impact of the recent leadership transition on our ability to attract and retain talent and to successfully execute on our "*Alnylam P^{5}x25*" strategy; our ability to discover and develop novel drug candidates and delivery approaches, including using our IKARIA and GEMINI platforms, and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates, including vutrisiran and patisiran; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including vutrisiran and patisiran, 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, AMVUTTRA and OXLUMO in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

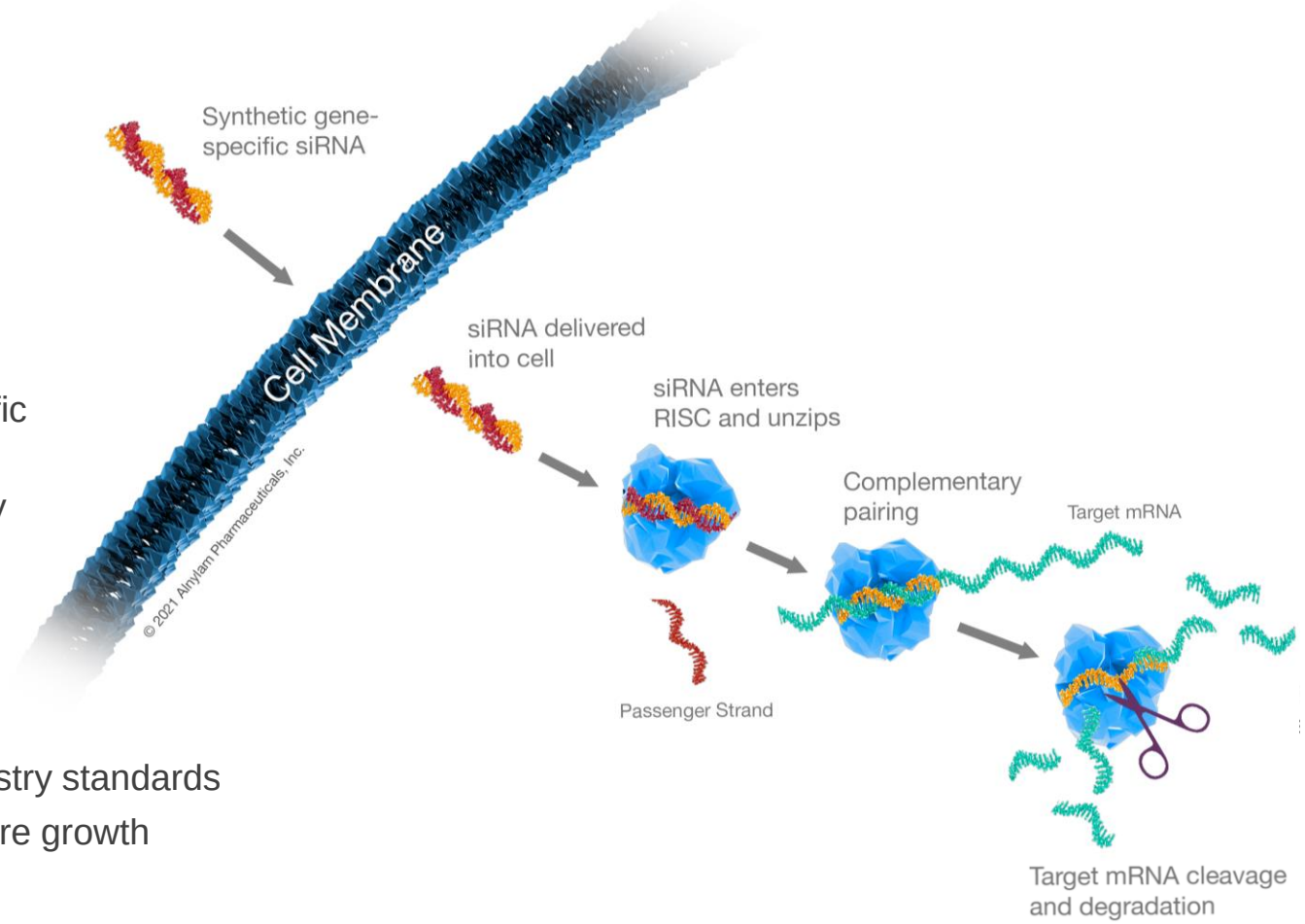
Alnylam Poised to Become a Top-Tier Biotech

Leader in RNAi Therapeutics

- Pioneered new class of innovative medicines
- 5 medicines approved in < 4 years
- Robust clinical pipeline across rare and prevalent diseases
- Global footprint with strong commercial capabilities
- Leading IP estate with fundamental, delivery, and product-specific patent protection
- 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

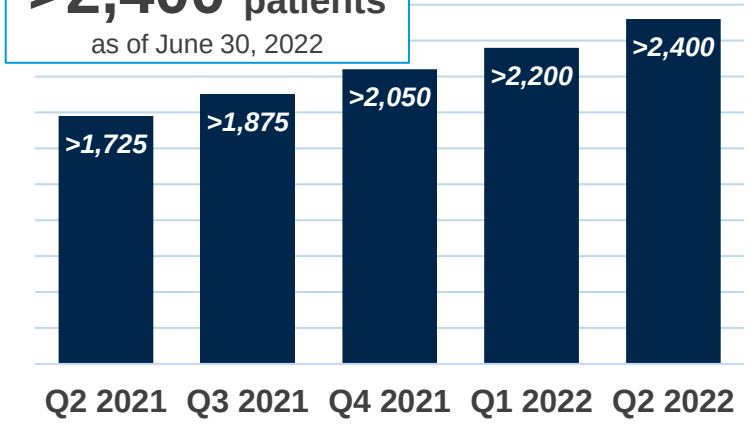


Continuing Global Commercial Execution

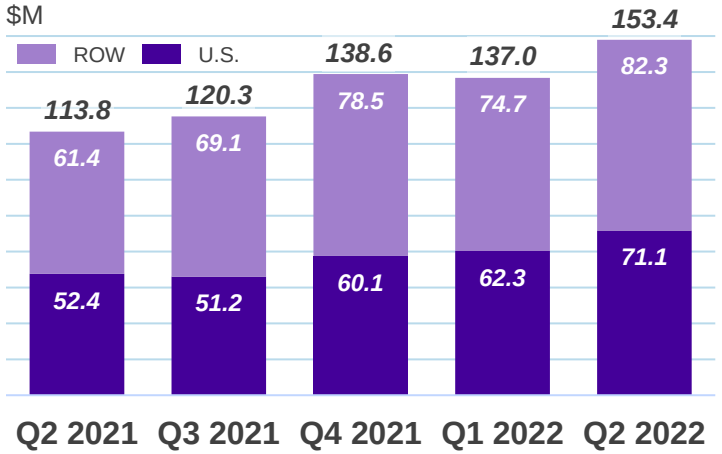
Q2 Commercial Performance Reflects Continued Steady Patient Growth

onpattro® (patisiran) lipid complex injection 10 mg/5 mL

>2,400 patients
as of June 30, 2022

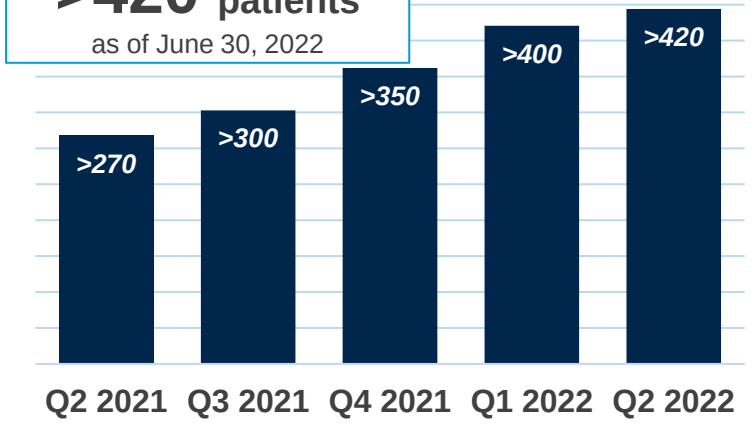


$153M
Q2 2022 revenues

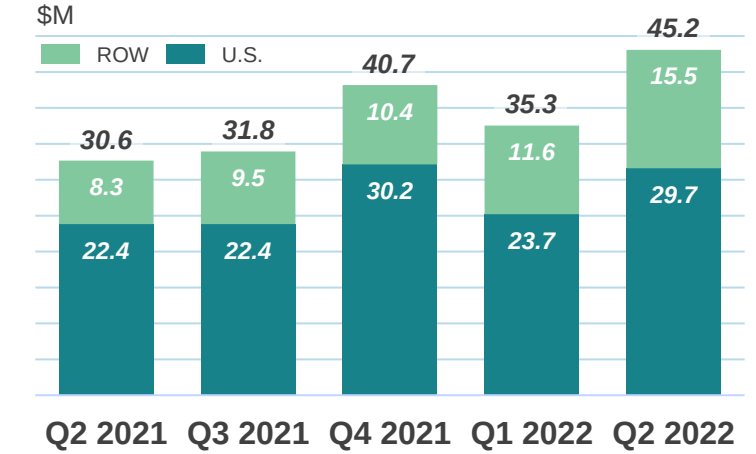


GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

>420 patients
as of June 30, 2022

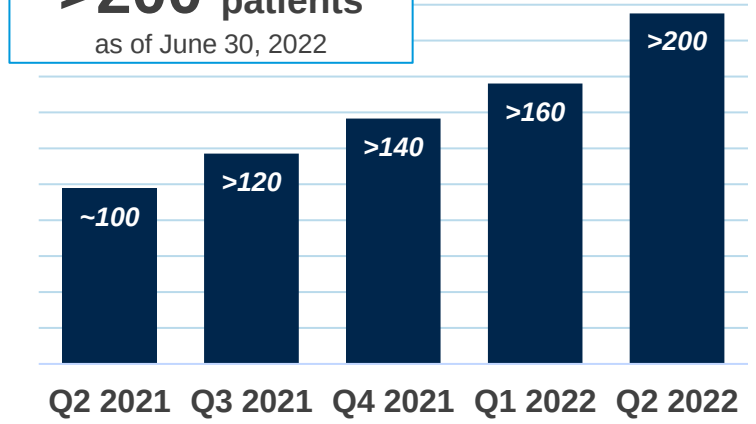


$45M
Q2 2022 revenues

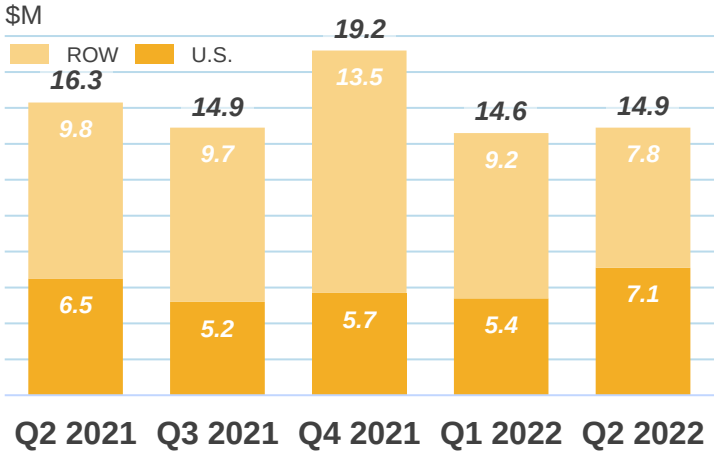


OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

>200 patients
as of June 30, 2022



$15M
Q2 2022 revenues



AMVUTTRA® (vutrisiran) Update: Initial Launch Progress

Promising Early Indicators Following U.S. Approval on June 13

PERFORMANCE

HCP & PATIENT OUTREACH

HEALTH SYSTEMS & PAYERS

EARLY HIGHLIGHTS

Encouraging early demand signal

- 133 Start Forms received from launch through July 22, 2022*
  - ~1/3 from new patients / ~2/3 from ONPATTRO switch
  - >20% sourced from new prescribers
- Product available in channel from early July

Initial promotion / education efforts

- >61,000 HCPs and Patients reached with launch messages within 48 hours
- Peer to peer educational programs underway reaching hundreds of physicians

Positive payer interactions

- ~60% of top tier Health Systems have initiated the formulary process
- 1st payer policy published (~24M covered lives)
- Anticipate permanent J-code will be established January 1, 2023

* Start Forms are an incomplete picture of U.S. demand
AMVUTTRA is approved in the U.S. for the PN of hATTR amyloidosis in adults

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

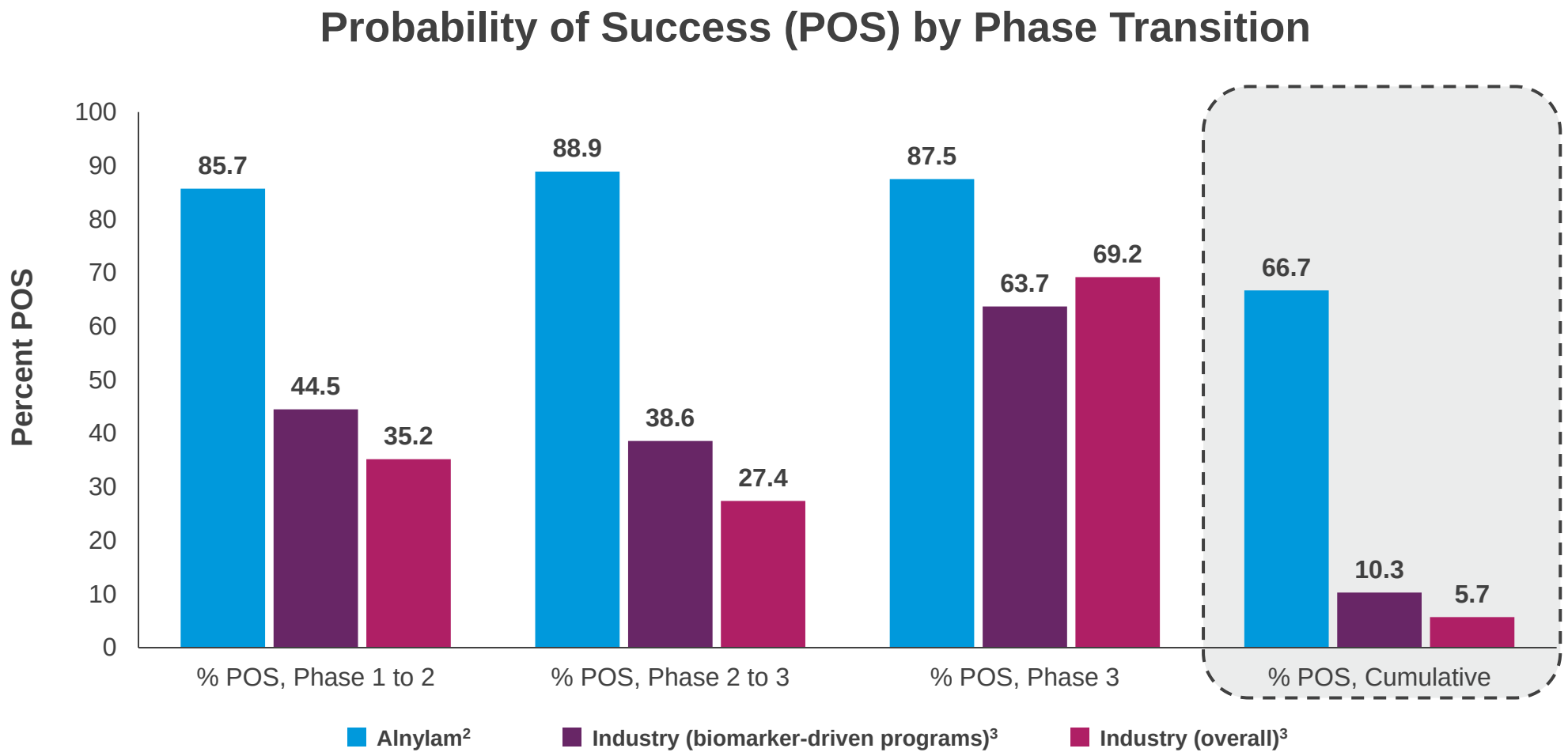
		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis with PN[2]*			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria[3]*			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1[4]*			●	Global
LEQVIO (inclisiran)	*Hypercholesterolemia[5]*			●	Milestones & up to 20% Royalties[6]
amvuttra (vutrisiran)	*hATTR Amyloidosis with PN[7]*			●	Global
Patisiran	*ATTR Amyloidosis with CM*		●		Global
Vutrisiran	*ATTR Amyloidosis with CM*		●		Global
Vutrisiran[8]*	*Stargardt Disease*		○		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Renal Stones*	●		●	Global
Cemdisiran (+/- Pozelimab)[9]*	*Complement-Mediated Diseases*		●		50-50; Milestone/Royalty
Belcesiran[10]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[11]*	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT)*	*Hypertension*	●			Global
ALN-HSD*	*NASH*	●			50-50
ALN-APP*	*Alzheimer's Disease;* *Cerebral Amyloid Angiopathy*	●			50-50
ALN-XDH*	*Gout*	●			Global

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for 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 stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; [5] 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; [6] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [7] Approved in the U.S. for the PN of hATTR amyloidosis in adults [8] Phase 3 study of vutrisiran in Stargardt Disease expected to initiate in late 2022; [9] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [10] Dicerna is leading and funding development of belcesiran; [11] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of September 2022

High-Yield Productivity of Alnylam RNAi Therapeutics Platform

Comparison of Historical Industry Metrics to Alnylam Portfolio[1]



[1] Analysis as of August 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

2022 Expected to Deliver Multiple Catalysts with Value-Creation Potential

Full 18-Month HELIOS-A Phase 3 Results with Vutrisiran	Early 2022 ✓
Cemdisiran Phase 2 Data in IgA Nephropathy	Early 2022 ✓
FDA Approval of Vutrisiran	Mid-2022 ✓
APOLLO-B Phase 3 Results with Patisiran	Mid-2022 ✓
ALN-HSD Phase 1 Part B Topline Results in NASH Patients	Mid-2022
Vutrisiran Biannual Dose Regimen Data	Late 2022
ALN-APP Phase 1 Topline Results	Late 2022
ALN-XDH Phase 1 Topline Results	Late 2022

Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4

Alnylam P5X25

Patients: Over 0.5 million on Alnylam RNAi therapeutics globally

Products: 6+ marketed products in rare and prevalent diseases

Pipeline: Over 20 clinical programs, with 10+ in late stages and 4+ INDs per year

Performance: ≥40% revenue CAGR through YE 2025

Profitability: Achieve sustainable non-GAAP profitability within period

Multiple Drivers of Future Growth

TTR Franchise Leadership

Expansion into Prevalent Diseases

Engine for Sustainable Innovation

Andreas (Sweden)
Diagnosed with hATTR amyloidosis

Catalania (Spain)
Diagnosed with hATTR amyloidosis

ATTR Amyloidosis

Rare, Progressively Debilitating, and Fatal Disease

Description

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

Hereditary ATTR (hATTR) Amyloidosis

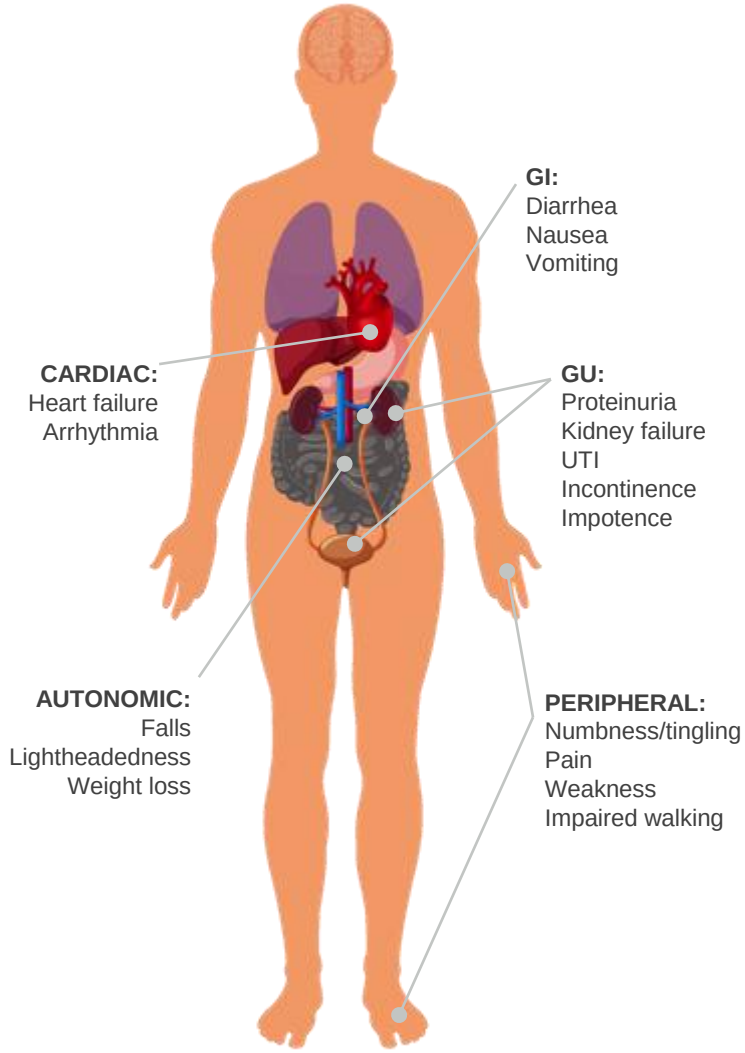
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

patients worldwide



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

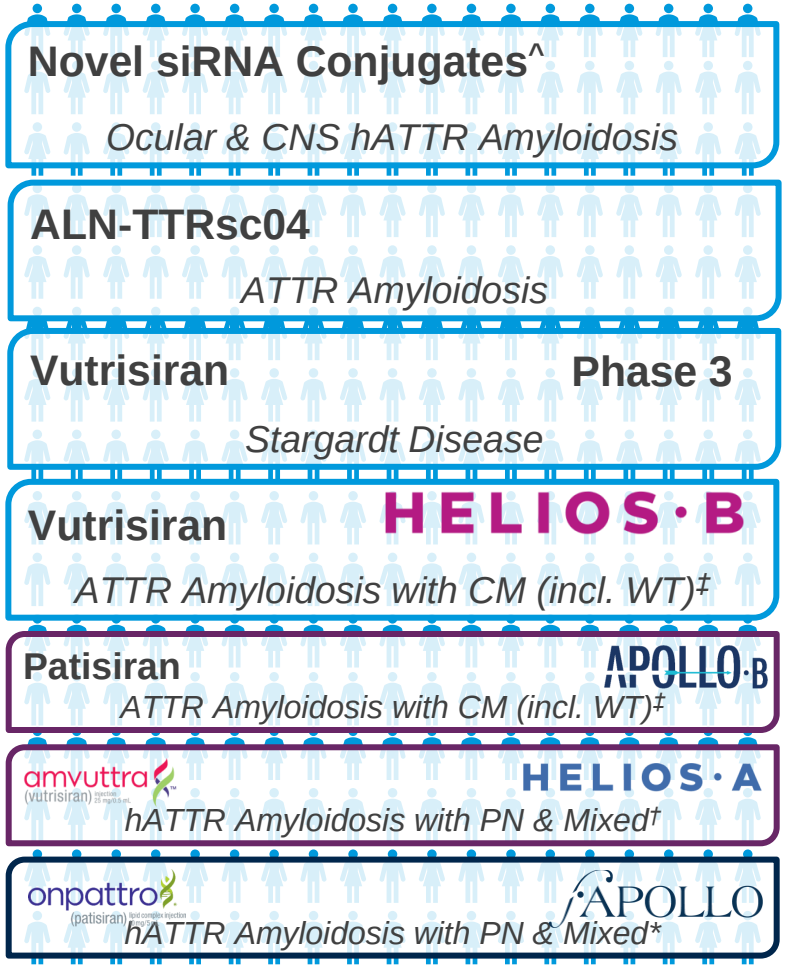
* Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012 (includes hATTR amyloidosis patients with polyneuropathy and cardiomyopathy)

Alnylam TTR Franchise

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

2020 – 2022

2022 – 2024



2024 & Beyond

* ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; ‡ ONPATTRO and AMVUTTRA have not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population

† AMVUTTRA is approved in the U.S. for the treatment of the PN of hATTR amyloidosis in adults; ^ Novel siRNA conjugate development candidates for ocular or CNS hATTR amyloidosis not yet selected

Intended to be illustrative and not intended to represent specific estimates of patient numbers

Patisiran APOLLO-B Phase 3 Study

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

N = 360
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
  - With or without background TTR stabilizer
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤III; minimum walk and NT-proBNP limits at baseline

1:1 RANDOMIZATION

Patisiran
IV q3w†
0.3 mg/kg

or

Placebo
IV q3w†

Primary Endpoint

- Change in 6-MWT at 12 months

Secondary Endpoints

- Cardiomyopathy symptoms and health status (KCCQ)
- Death and hospitalization outcomes*

Selected Exploratory Endpoints

- Cardiac biomarkers

Open-Label Extension

ClinicalTrials.gov Identifier: NCT03997383

APOLLO-B

Results presented at ISA – Sept 2022

Additional results to be presented at HFSA – Sept 2022

sNDA filing expected in **late 2022**

Concomitant use of local standard of care allowed during study, including TTR stabilizer

† To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min. before each study drug infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers

NYHA: New York Heart Association; NT-proBNP: N-terminal pro b-type natriuretic peptide; 6-MWT: 6-Minute Walk Test

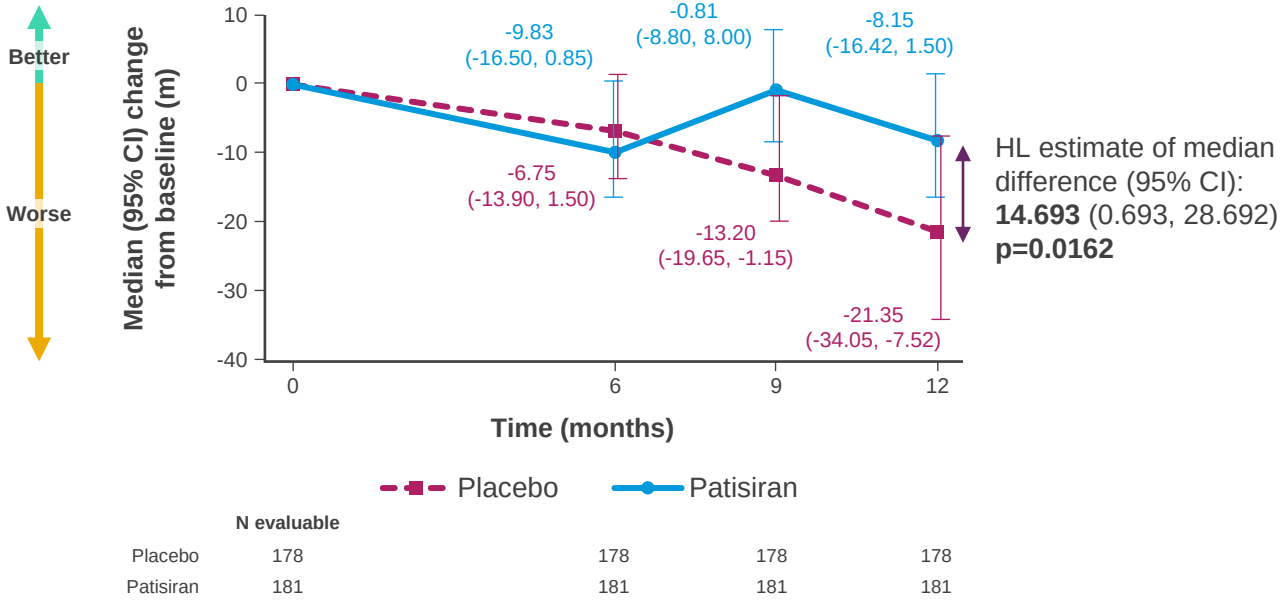
* Composite all-cause mortality, frequency of CV events, and change from baseline in 6-MWT; Composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in patients not on tafamidis at baseline; Composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in overall population

APOLLO-B Phase 3 Study Results

Primary and First Secondary Endpoints

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

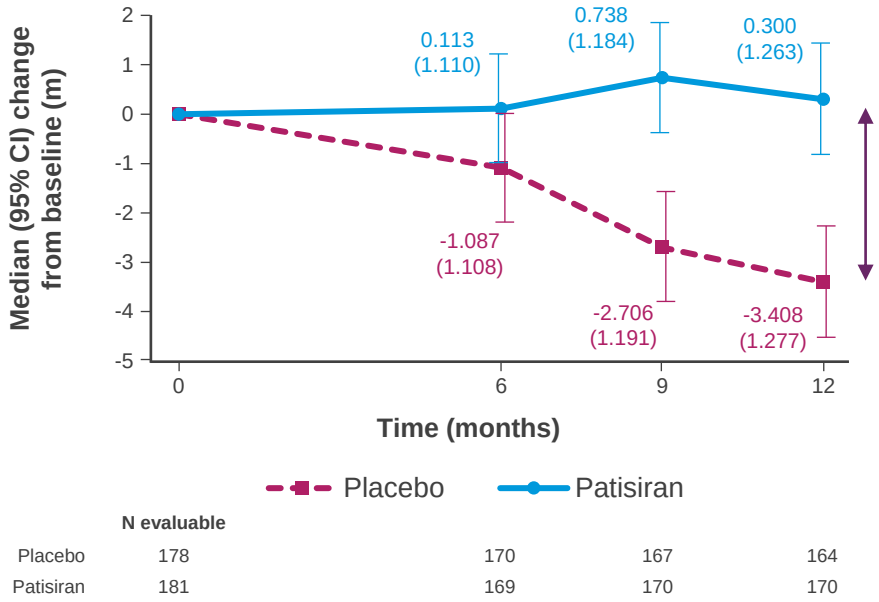
Change from Baseline in 6-MWT[a]



HL estimate of median difference (95% CI): **14.693** (0.693, 28.692) **p=0.0162**

N evaluable				
Placebo	178	178	178	178
Patisiran	181	181	181	181

Change From Baseline in KCCQ-OS using MMRM[b]



LS mean (SEM) difference: **3.709** (1.796) **p=0.0397**

N evaluable				
Placebo	178	170	167	164
Patisiran	181	169	170	170

[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.

APOLLO-B Phase 3 Study Results

Overall and Cardiac Safety Summary[a]

- Majority of AEs were mild or moderate in severity
- AEs ≥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

At least one event, n (%)	Patisiran (n=181)	Placebo (n=178)
AEs	165 (91.2)	168 (94.4)
SAEs	61 (33.7)	63 (35.4)
Severe AEs	47 (26.0)	52 (29.2)
AEs leading to treatment discontinuation	5 (2.8)	5 (2.8)
Deaths (safety analysis)[b]	5 (2.8)	8 (4.5)
Deaths (efficacy analysis)[c]	4 (2.2)	10 (5.6)
Cardiac disorders (system organ class)[d]	82 (45.3)	100 (56.2)
Cardiac arrhythmia high-level group term	35 (19.3)	48 (27.0)
Supraventricular arrhythmias (including atrial fibrillation)	24 (13.3)	36 (20.2)
Ventricular arrhythmias and cardiac arrest	5 (2.8)	8 (4.5)
Cardiac conduction disorders	8 (4.4)	10 (5.6)
Rate and rhythm disorders not elsewhere classified	5 (2.8)	4 (2.2)
Cardiac failure SMQ (broad)	69 (38.1)	84 (47.2)
QT Prolongation /Torsade de pointes SMQ[e]	12 (6.6)	18 (10.1)

[a] Safety is reported for the 12-month double-blind treatment period. b Deaths in the patisiran arm included sudden cardiac death, undetermined death, death due to HF, and death due to pancreatitis. c Efficacy analysis of deaths presented in accordance with pre-defined statistical analysis plan, which excluded deaths due to COVID-19 (1 patisiran patient) and treated cardiac transplant as death (2 placebo patients). d Based on MedDRA "Cardiac Disorders" System Organ Class. e There were no identified cases of Torsade de pointes. Abbreviations: AE, adverse event; QT, QT interval; SAE, serious adverse event; SMQ, Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query.

Vutrisiran HELIOS·B Phase 3 Study

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

N ~ 600
Patient Population

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

1:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Primary Endpoint

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

Select Secondary Endpoints

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

ClinicalTrials.gov Identifier: NCT04153149

HELIOS·B

Enrollment complete

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

Study includes optional interim analysis

Stargardt Disease

Promising New Opportunity for Vutrisiran

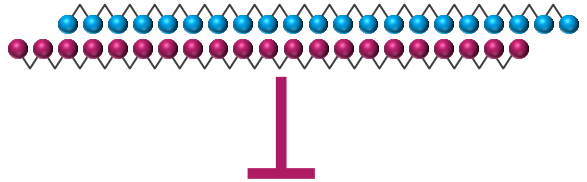
Description

Rare, inherited, progressive form of blindness caused by accumulation of toxic vitamin A metabolites in retina leading to central vision loss

High unmet medical need with no approved treatments

Incidence of 1 in 8,000-10,000

Therapeutic Hypothesis



Silence
production of TTR in liver*

Reduce
circulating TTR / RBP4 / Vitamin A Complex

Reduce
build-up of toxic metabolites in retina

Halt Progression
of vision loss

* >95% of TTR in circulation produced in liver

Multiple Drivers of Future Growth

- TTR Franchise Leadership
- Expansion into Prevalent Diseases
- Engine for Sustainable Innovation

RNAi Therapeutics Profile Supports Potential Expansion to Prevalent Diseases

- Durability
- Clamped pharmacology
- Safety profile evaluated in clinical trials
- Improved access

RARE

ONPATTRO: hATTR w/ PN[1]
GIVLAARI
OXLUMO: PH1
AMVUTTRA: hATTR w/ PN[2]
Fitusiran
Belcesiran
ALN-HTT

SPECIALTY

Patisiran: ATTR w/ CM[3]
Vutrisiran: ATTR w/ CM[3]
Cemdisiran

PREVALENT

Leqvio® (inclisiran)[4]
Zilebesiran (ALN-AGT)
ALN-HBV02 (VIR-2218)
Lumasiran: Recurrent stones
ALN-HSD
ALN-APP
ALN-XDH
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; [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.

Capabilities Support Potential Expansion to Prevalent Diseases

Sophisticated, Scalable, and Global Medical and Commercial Organizations

RARE

ONPATTRO: hATTR w/ PN[1]
GIVLAARI
OXLUMO: PH1
AMVUTTRA: hATTR w/ PN[2]
Fitusiran
Belcesiran
ALN-HTT

SPECIALTY

Patisiran: ATTR w/ CM[3]
Vutrisiran: ATTR w/ CM[3]
Cemdisiran

PREVALENT

Leqvio® (inclisiran)[4]
Zilebesiran (ALN-AGT)
ALN-HBV02 (VIR-2218)
Lumasiran: Recurrent stones
ALN-HSD
ALN-APP
ALN-XDH
ALN-KHK

Scalable Capabilities

- **Patient Support:** Experienced patient support teams have enabled >90% adherence in the U.S.
- **Customer Engagement:** High-science customer-facing field teams with strong leadership
- **Access:** World renowned partnerships with key payers, with VBAs covering >95% of eligible lives in the U.S.
- **Diagnosis:** Support for independent diagnostic programs
- **Global Footprint:** 23 Direct and 24 distributor markets (and growing) with 50% revenues generated ex-U.S.

[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; [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.

Reimagining Treatment of Prevalent Diseases

Highly Differentiated, Infrequently Administered Therapies Against Validated Targets

COMMERCIAL

LEQVIO® (inclisiran) injection 284 mg/1.5 mL

Hypercholesterolemia*
- Biannually dosed lipid lowering therapy with effective and sustained LDL-C reduction of up to 52%
- Potential to reduce ASCVD risks through lowering of LDL-C at population level

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PHASE 2

Zilebesiran

Hypertension
- Targets AGT with potential to achieve tonic blood pressure control and improve medication adherence
- Demonstrated >20 mmHg BP reduction in Phase 1, with opportunity to impact CV outcomes at population level

ALN-HBV02 (VIR-2218)

Chronic Hepatitis B Virus (HBV) Infection
- Targets conserved region in X gene, with multi-log reductions in HBsAg levels in Phase 1/2 studies
- Opportunity to be foundational therapy with potential to achieve functional cure

Lumasiran

Recurrent Kidney Stone Disease
- Targets GO1 to lower production of calcium oxalate crystals, source of most kidney stones in adults
- Reductions in kidney stone event rate and nephrocalcinosis in PH1 observed in Phase 3 program

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PHASE 1

ALN-HSD

Nonalcoholic Steatohepatitis (NASH)
- LOF mutations in HSD17B13 associated with reduced risk of liver injury among NAFLD patients
- Potential to reduce cirrhosis and end-stage liver disease

ALN-XDH

Gout
- XDH is genetically and clinically validated target for urate lowering
- Potential for more consistent disease management leading to fewer gout flares and less joint damage

Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; Vir is leading and funding development of ALN-HBV02; With the exception of Leqvio® (inclisiran), these are investigational agents and have not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding their safety or effectiveness. * 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.

RNAi Therapeutics Could Potentially Reimagine Treatment of Hypertension

Opportunity for Tonic Blood Pressure (BP) Control

Disease Overview

Primary Hypertension[1]

~108 Million

in U.S.

Hypertension at high CV risk[2]

~38 Million

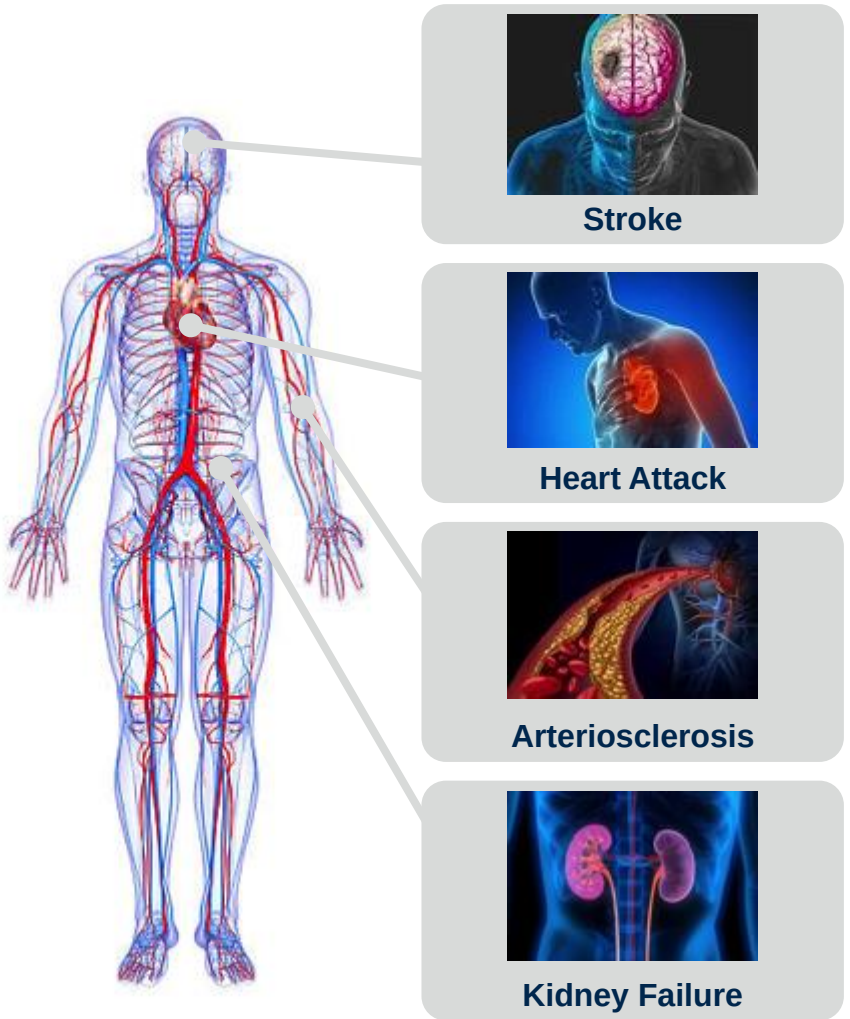
in U.S.

>71% of patients have uncontrolled hypertension (>130/80 despite treatment)[3]

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



[1] Centers for Disease Control and Prevention (CDC). Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria From the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2013–2016. Atlanta, GA: US Department of Health and Human Services; 2019.

[2] Estimated from multiple sources and internal estimates: Dorans. JAHA. 2018; Al Kibria. Hypertens Res. 2019; CDC Hypertension Cascade. 2019; High CV risk: ASCVD risk score ≥20% and/or history of CVD

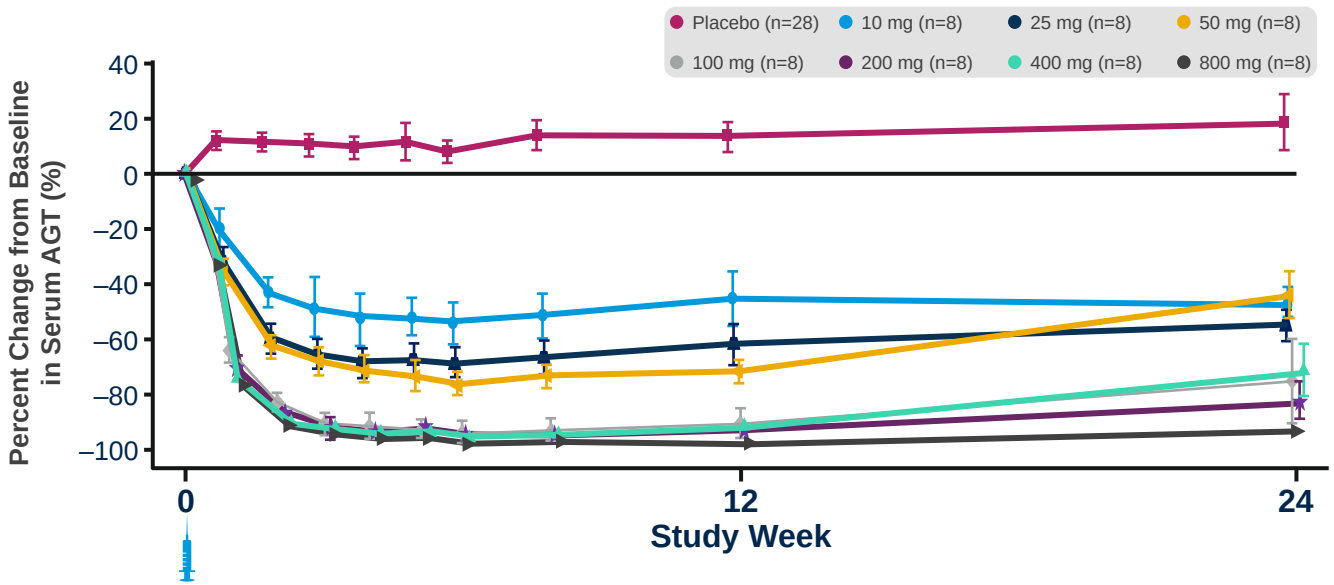
[3] U.S. Department of Health and Human Services. The Surgeon General's Call to Action to Control Hypertension. Washington, DC: U.S. Department of Health and Human Services, Office of the Surgeon General; 2020.

Zilebesiran (ALN-AGT) Interim Phase 1 Results

Results for Investigational Therapy Presented at AHA Scientific Sessions[1]

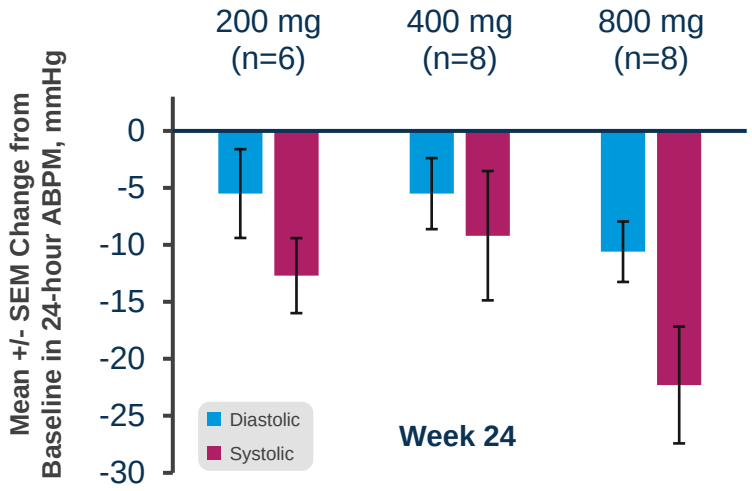
Dose-Dependent and Durable Reduction of Serum AGT ≥90% Sustained for 12 Weeks After Single Doses of zilebesiran ≥100 mg

Serum AGT reductions of >90% maintained through six months after single dose of 800 mg



Sustained Reductions in SBP and DBP[2]

Mean 24h blood pressure reduction of >20 mm Hg at Month 6 after a single dose of 800 mg



Encouraging safety and tolerability profile

- Most AEs mild or moderate in severity
- ISRs in 5 of 56 patients (8.9%) were all mild and transient
- No treatment-related SAEs
- No patients required intervention for low blood pressure

KARDIA-1 Phase 2 Study enrollment completion expected **early 2023** with topline data **mid-2023**

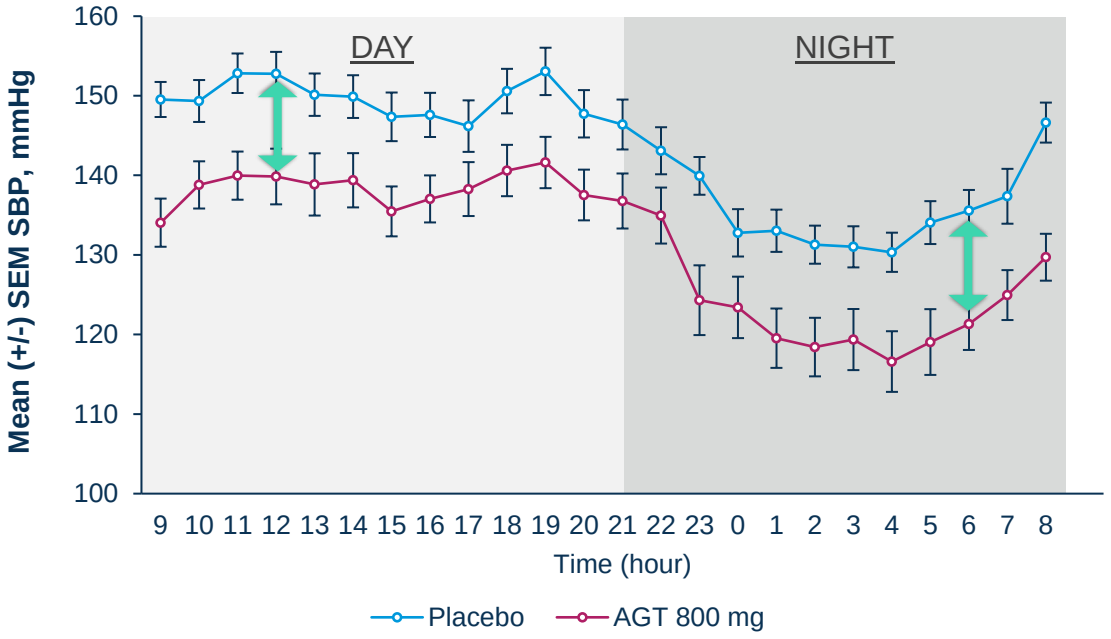
KARDIA-2 Phase 2 Study enrollment completion expected **at or around year-end 2022**

[1] Huang et al, AHA, November 2021; Data cutoff date: 28 May 2021

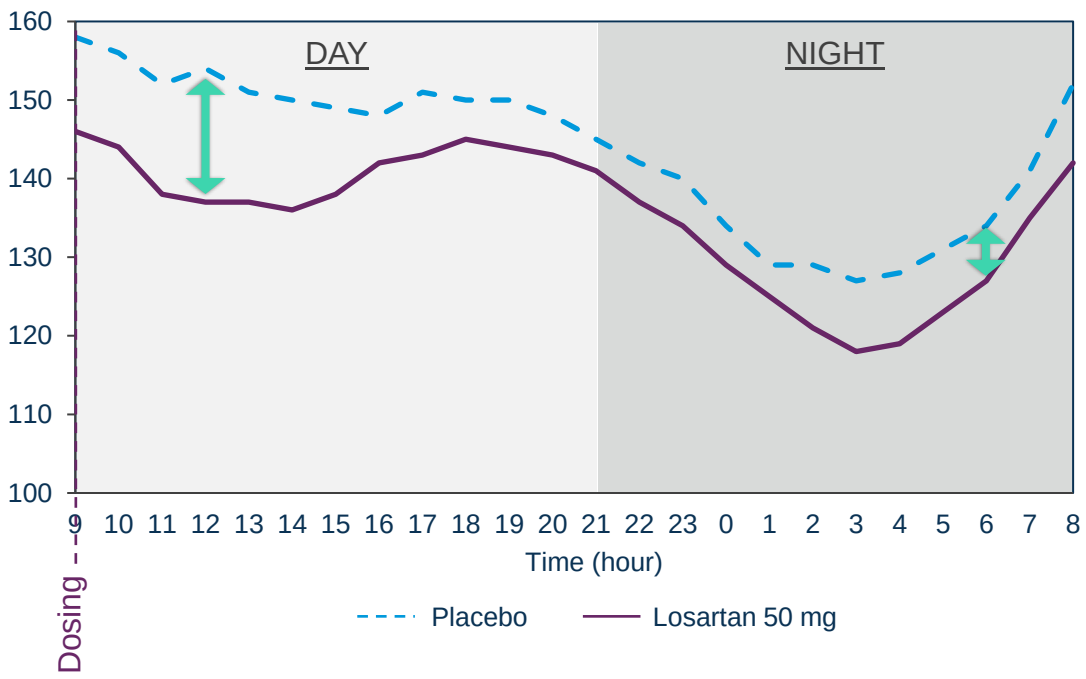
[2] SBP: systolic blood pressure; DBP: diastolic blood pressure

Early Evidence of Tonic BP Control Over 24 Hours with Zilebesiran

Zilebesiran: 24-Hour SBP at Week 6



Losartan: 24-Hour SBP at Week 4[a]



Huang AH, Taubel J, Desai AS, et al., AHA Scientific Sessions 2021

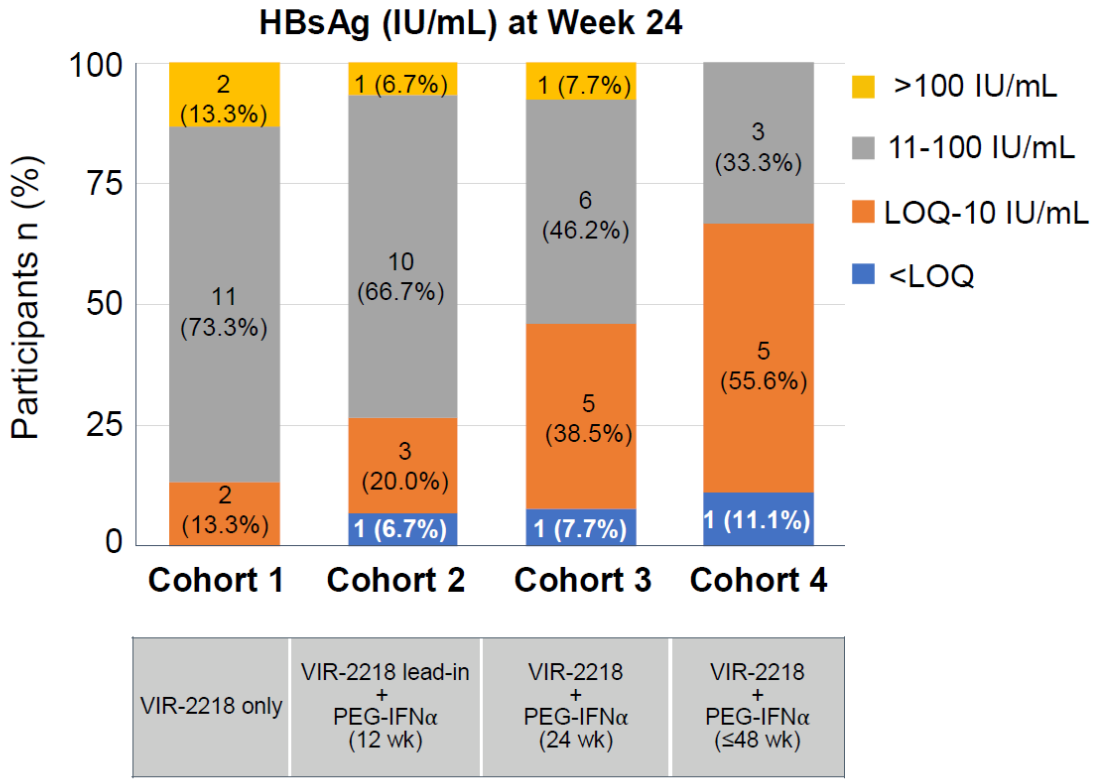
[a] Adapted from Fogari et al. (1999) Current Therapeutic Research 60(4):195-206

AGT, angiotensinogen; BP, blood pressure; SBP, systolic blood pressure

HBV: Global Health Problem Impacting Developed and Developing Countries

Ongoing VIR-2218 Phase 2 Study Evaluating Impact of Concomitant PEG-IFNα in Chronic HBV

Significant Proportion Achieve HBsAg <10 IU/mL, Including <LOQ



- VIR-2218 alone or in combination with PEG-IFNα has been generally well tolerated
- All VIR-2218 plus PEG-IFNα regimens were associated with clinically meaningful HBsAg reductions (> 2 log10IU/mL on average) by Week 24
- Three participants receiving VIR-2218 and PEG-IFNα achieved HBsAg loss by Week 24; 2 of 3 achieved anti-HBs seroconversion

Alnylam Opt-in Right to VIR-2218 Prior to Phase 3

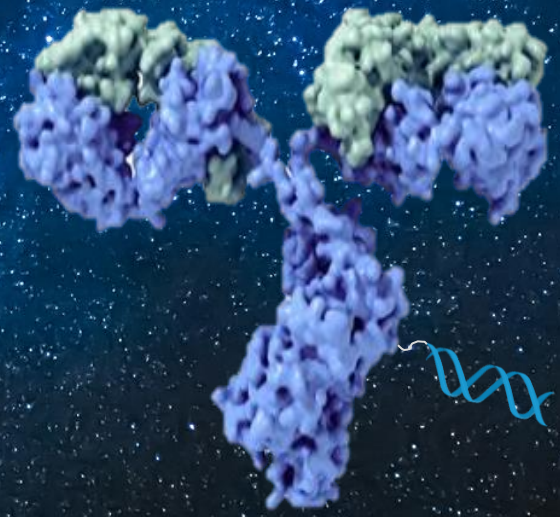
Yuen et al., *AASLD*, November 2021

Multiple Drivers of Future Growth

TTR Franchise Leadership

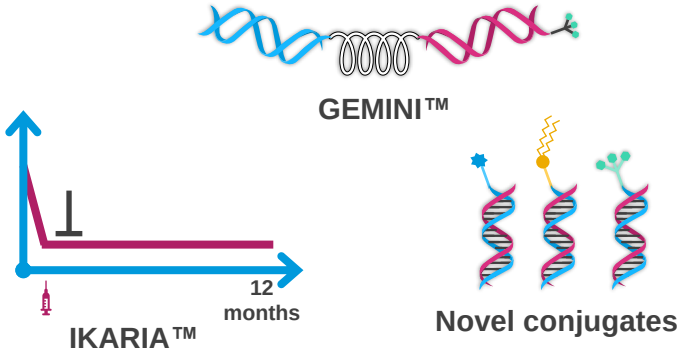
Expansion into Prevalent Diseases

Engine for Sustainable Innovation



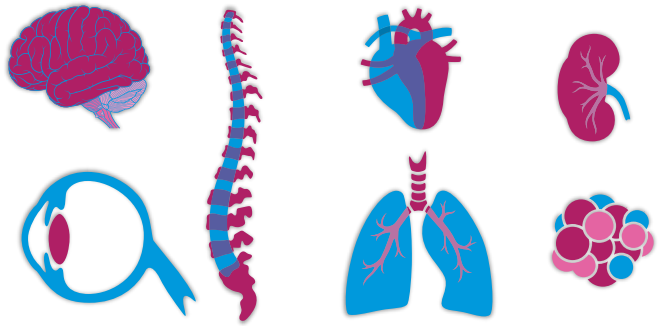
Sources of Sustainable Innovation

Platform Innovation



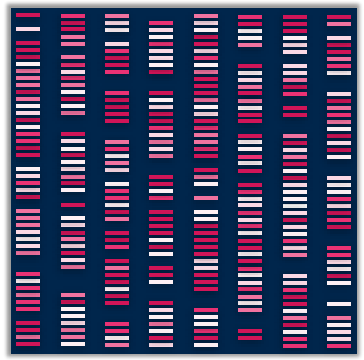
- Two-decade track record of industry leadership in RNAi
- GEMINI™ combines siRNAs for simultaneous silencing of two transcripts
- IKARIA™ enables robust target knockdown with annual dosing potential
- Novel conjugates with variety of ligands for delivery beyond liver

Extrahepatic Delivery



- Potential for delivery to range of organs
- C16 conjugate provides robust CNS knockdown with wide biodistribution and long duration of action
- Peptide and antibody-based approaches being explored for targeted siRNA delivery to new tissues

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 (e.g., *HSD17B13, INHBE*, and more)

Potential to Potently, Durably, Safely and Conveniently Suppress Two Targets

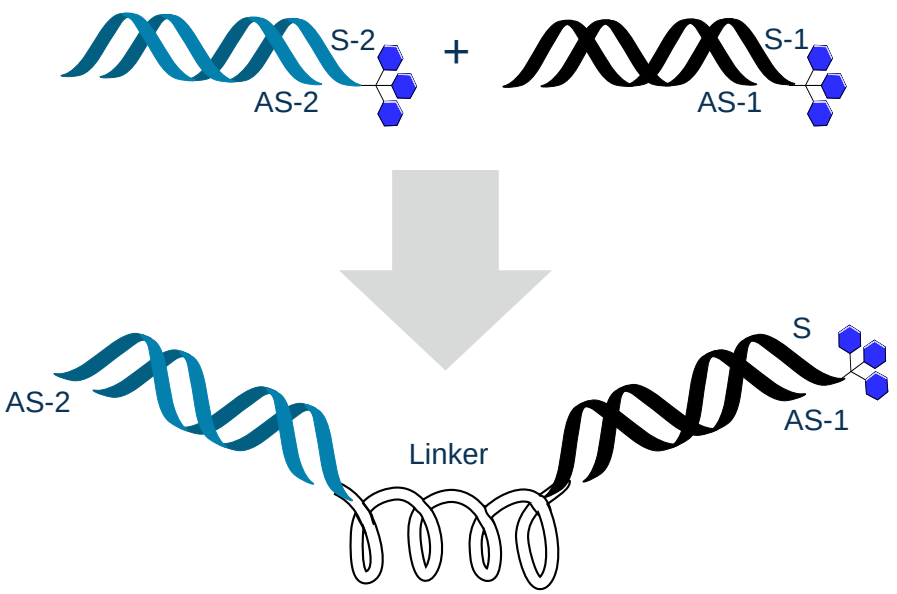
GEMINI

Platform

- Goal of silencing two gene transcripts using single chemical entity
- Ensures uptake of both siRNAs in same cell
- Potentially simplified development path vs. two entities or combination
- Potential to address polygenic diseases (e.g., cardiometabolic, CNS)

GEMINI-CVR Program: Reimagining Treatment of CV Disease

- siRNA 1 targets ANGPTL3 (genetically validated to reduce atherogenic lipids); siRNA 2 targets angiotensinogen (pharmacologically validated to reduce blood pressure)
- Targets support potential to prevent major adverse cardiac outcomes in high-risk individuals
- Biannual or annual subQ injection in office or pharmacy administration
- Targets ≥40% reductions in LDL-C and triglycerides, >10 mmHg reduction in systolic blood pressure and safety profile appropriate for broad use
- Development candidate targeted for 2023



ALN-APP: First Investigational RNAi Therapeutic for CNS

New Potential Approach in Alzheimer's Disease and Cerebral Amyloid Angiopathy

Proprietary C16 conjugate for delivery to CNS

- IT administration, anticipating infrequent dosing (Q3-6M or less)

APP is a genetically validated target for two CNS diseases

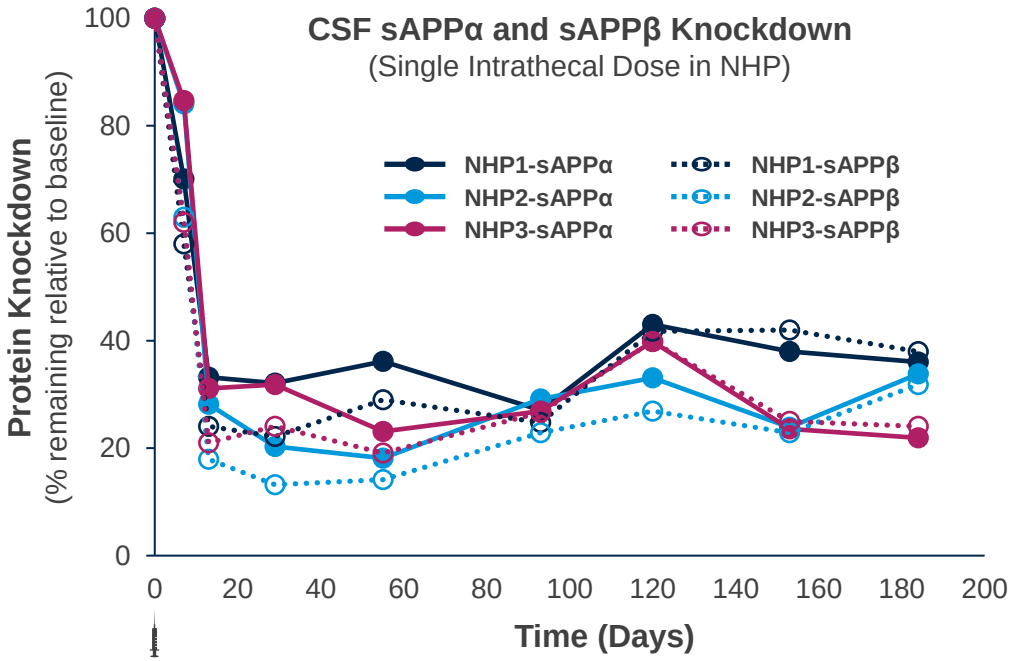
- Mutations and duplications in *APP* gene cause Alzheimer's disease (AD), cerebral amyloid angiopathy (CAA), or both
- Mutations that reduce production of APP cleavage products are protective against AD
- AD (most common cause of dementia) and CAA (second most common cause of intracerebral hemorrhage) represent large populations with high unmet need

Upstream of current approaches: First to target *APP* mRNA

- Expected to comprehensively lower all APP cleavage products, including Aβ, both intra- and extracellularly

CTA filed in late 2021

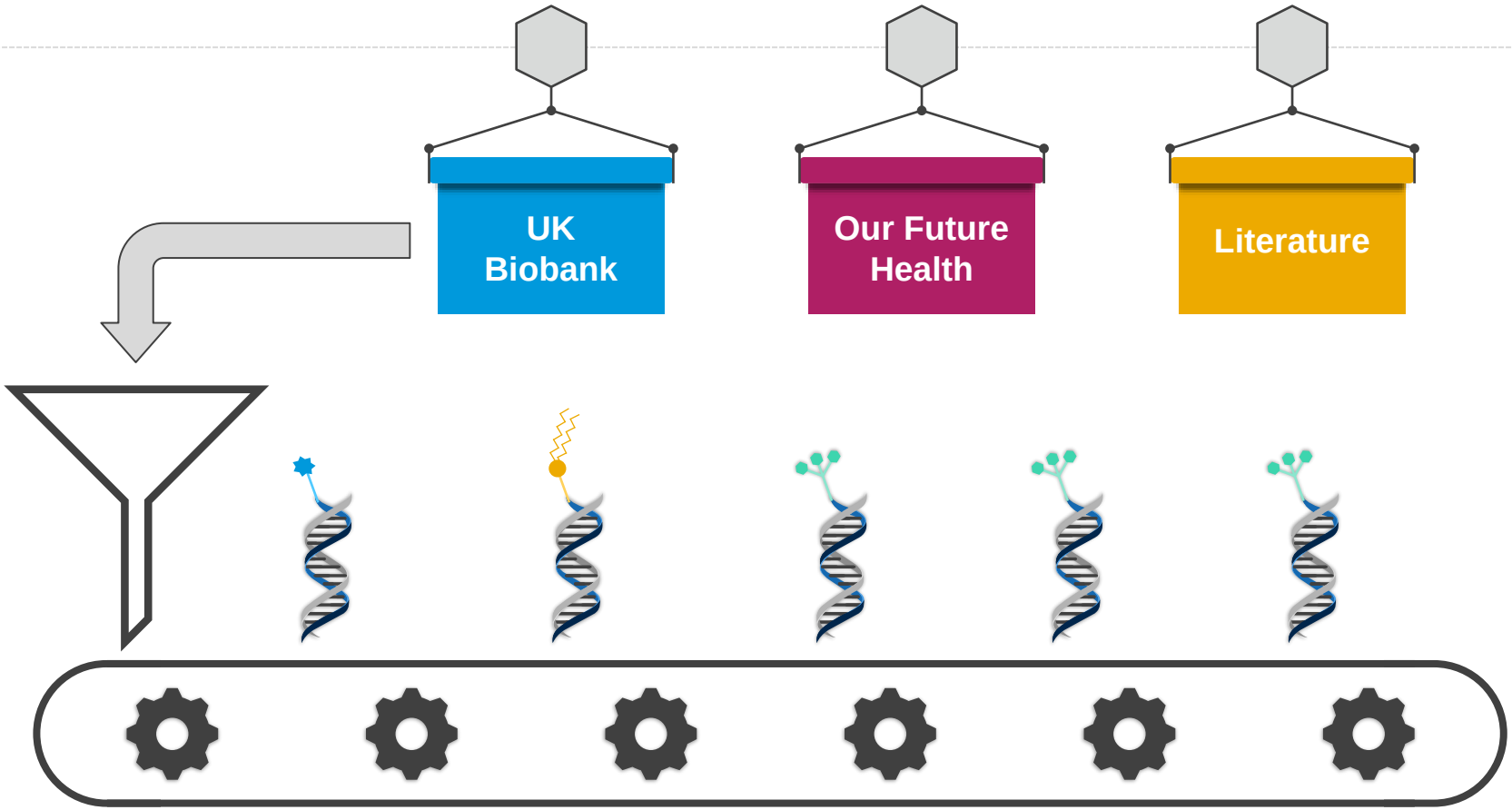
- Phase 1 initiated in early-onset AD patients in early 2022 with initial human data expected at or around year-end 2022



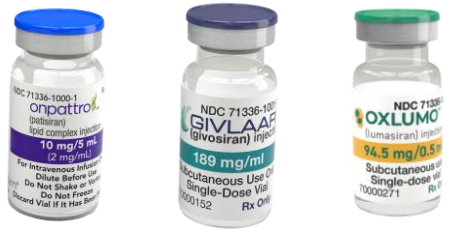
Potential "Firsts" with ALN-APP

- First siRNA to be delivered to CNS
- First C16 conjugate for CNS delivery
- First development program directly targeting *APP* mRNA
- First CNS collaboration program with Regeneron

Delivering Sustainable Innovation with RNAi Therapeutics



TRANSFORMATIVE MEDICINES



Alnylam 2022 Goals

			Early	Mid	Late
onpattro (patisiran) GIVLAARI (givosiran) OXLUMO (lumasiran) amvuttra (vutrisiran)		*Combined Net Product Revenue Guidance $870 million – $930 million*			●
PATISIRAN	hATTR/ATTR Amyloidosis	APOLLO-B Phase 3 Topline Results		✓	
		File sNDA for ATTR with cardiomyopathy			●
VUTRISIRAN*	hATTR/ATTR Amyloidosis	FDA Approval		✓	
		U.S. Launch		✓	
		EMA Approval		●	
		Biannual Dose Regimen Data			●
	Stargardt Disease	Initiate Phase 3 in Stargardt Disease			●
ALN-TTRsc04*	ATTR Amyloidosis	File IND			●
		Initiate Phase 1 Study			●
LUMASIRAN	PH1, Recurrent Renal Stones	Complete Enrollment in Phase 2 Study in Recurrent Renal Stones			●
INCLISIRAN	Hypercholesterolemia	FDA Approval (1/1/22 PDUFA)	✓		
CEMDISIRAN* (+/- POZELIMAB)	Complement-Mediated Diseases	Phase 2 Monotherapy Results in IgA Nephropathy	✓		
		Initiate Phase 3 Combination Study in PNH	✓		
ZILEBESIRAN*	Hypertension	Complete KARDIA-2 Enrollment (at or around year-end)			●
ALN-HBV02 (VIR-2218)*	Chronic HBV Infection	Phase 2 Combination Results	✓		●
ALN-HSD*	NASH	Phase 1 Part B Topline Results		●	
ALN-APP*	Alzheimer's Disease	Initiate Phase 1 Study	✓		
		Phase 1 Topline Results			●
ALN-XDH*	Gout	Initiate Phase 1 Study	✓		
		Phase 1 Topline Results			●
ADDITIONAL PROGRAMS		File 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 Culture to Ensure Future Success

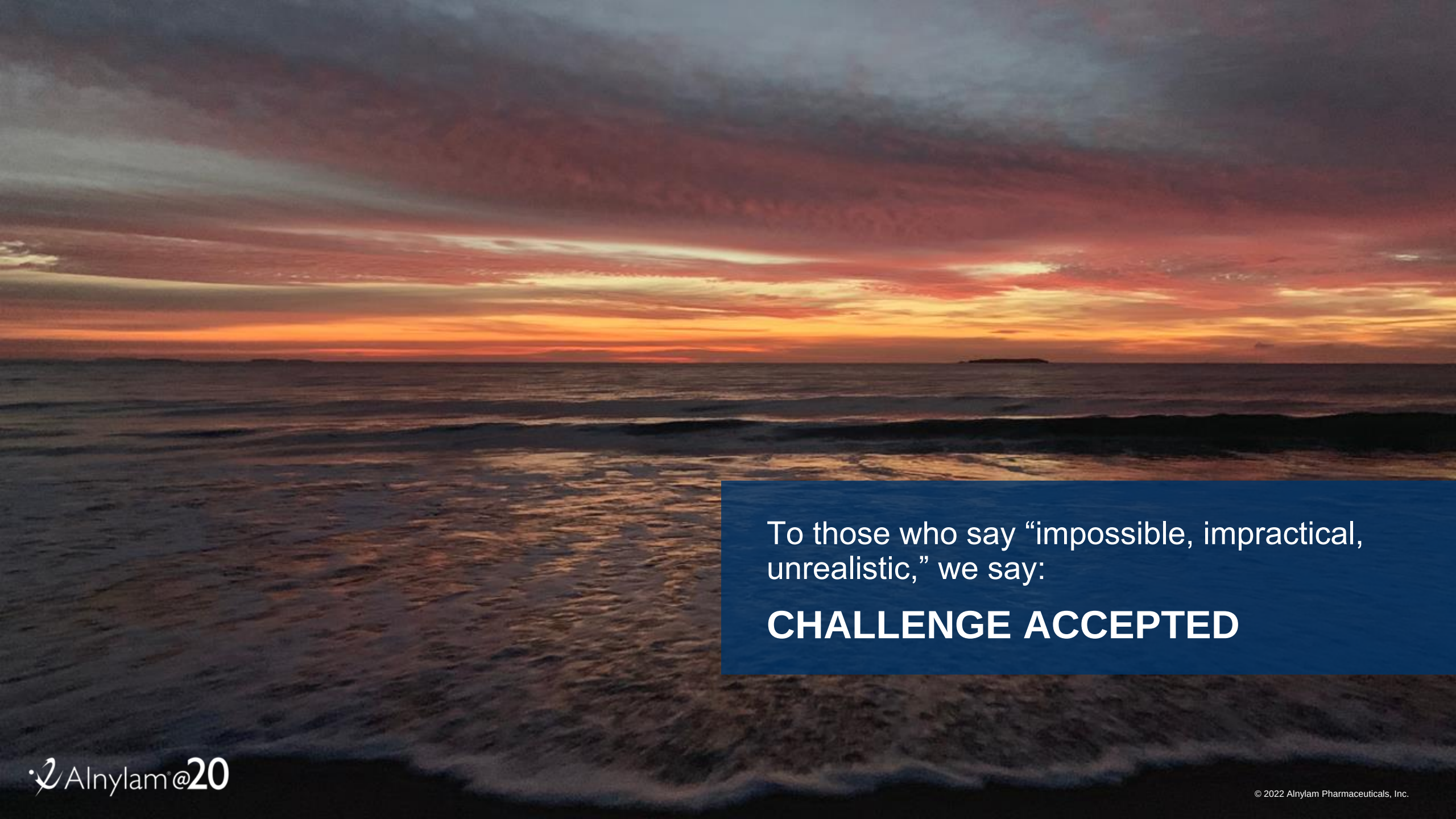
- Commitment to People
- Scientific Innovation
- Diversity, Equity, & Inclusion
- Social Responsibility

The Boston Globe TOP PLACES TO WORK 2015-2021

Science 2021 TOP EMPLOYER

FAST COMPANY BEST WORKPLACES FOR INNOVATORS 2022

Bloomberg Gender-Equality Index 2021



Alnylam@20