Nathan (USA)
Diagnosed with AHP

40th Annual J.P. Morgan Healthcare Conference

Yvonne Greenstreet, MBChB, MBA
Chief Executive Officer
January 10, 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 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, our preliminary fourth quarter and 2021 fiscal year global net product revenue and patients on therapy, the probability of success of our RNAi therapeutics platform, the drivers of our future growth potential, including the potential of our TTR franchise, our continued confidence in the design and ongoing execution of the APOLLO-B Phase 3 study and the evidence for investigational RNAi therapeutics in ATTR cardiomyopathy, 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. 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; the finalization and audit of our fourth quarter and 2021 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, 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; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including vutrisiran, 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 OXLUMO, ONPATTRO (and potentially vutrisiran, if approved) 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.

CELEBRATING 20 YEARS OF ALNYLAM LEADERSHIP AND WHAT'S NEXT IN THE RNAi Revolution

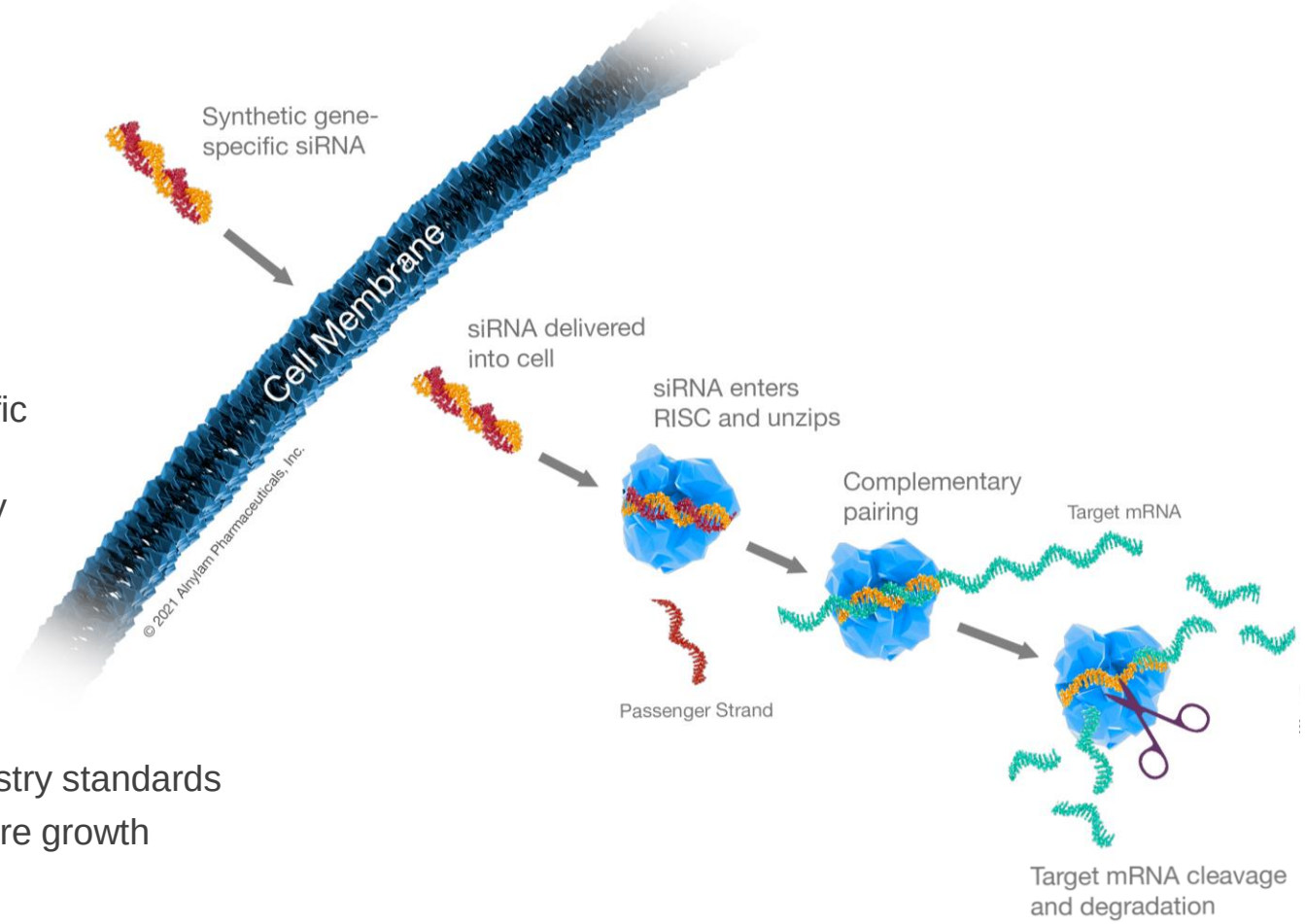
Alnylam Poised to Become a Top-Tier Biotech

Leader in RNAi Therapeutics

- Pioneered new class of innovative medicines
- 4 medicines approved in < 3 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



Notable Accomplishments in 2021

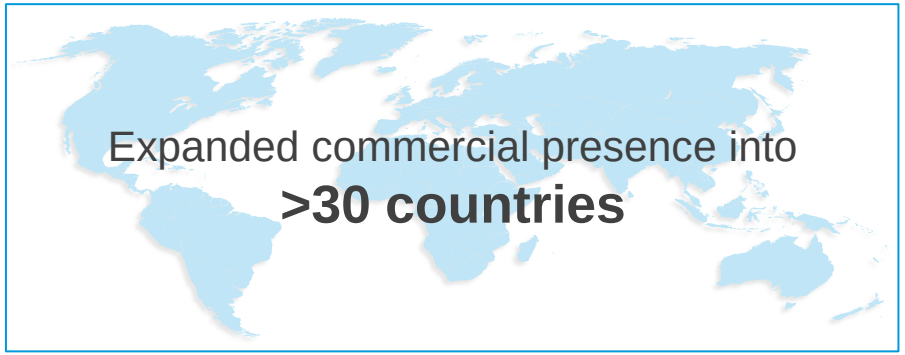
onpattro® (patisiran) lipid complex injection 10 mg/5 mL
GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL
OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

Combined net product revenues of
$662 million*
(83% growth YoY)

APOLLO-B HELIOS-B

Completed enrollment in two key Phase 3 studies in ATTR-CM

Advanced multiple investigational products for prevalent diseases (zilebesiran, ALN-HBV02, ALN-HSD)



Expanded commercial presence into
>30 countries

2 NDA/sNDA submissions (vutrisiran, OXLUMO®)

Alnylam P5x25

Launched new 5-year strategy

$

Maintained strong financial position

- **$2.4 billion in cash** at year-end 2021*
- **$100M+ YoY improvement** in non-GAAP operating loss 9/30 YTD

2 CTA filings (ALN-APP, ALN-XDH)

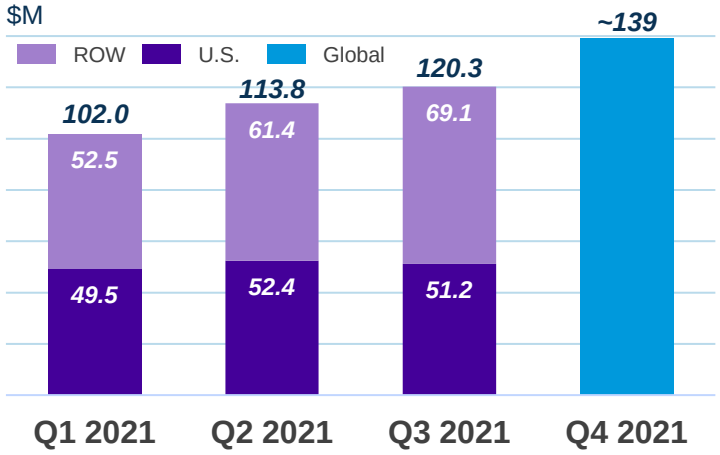
* Preliminary selected financial results are unaudited, subject to adjustment, and provided as an approximation in advance of the Company's announcement of complete financial results in February 2022.

Continuing Strong Global Commercial Execution

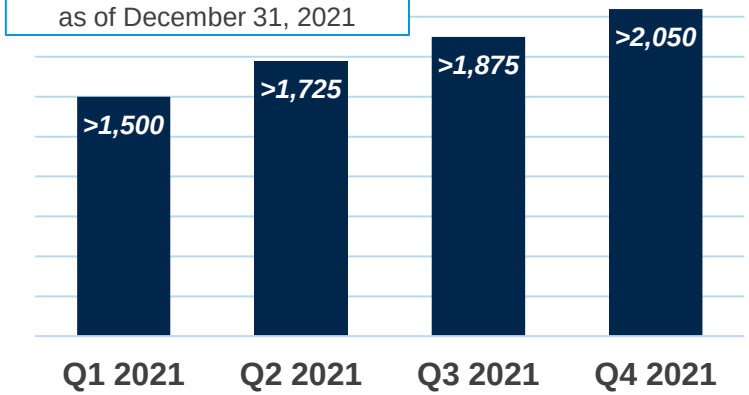
Combined Net Product Revenues ($662M) at Upper End of Guidance Range, with 83% YoY Growth*

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

~$475M
2021 revenues

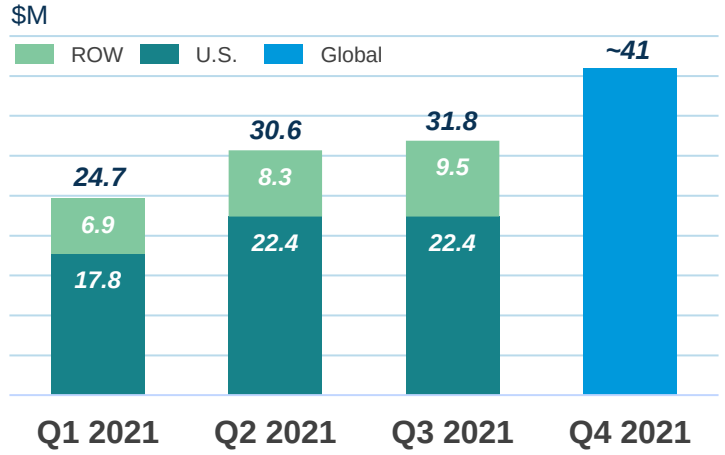


>2,050 patients
as of December 31, 2021

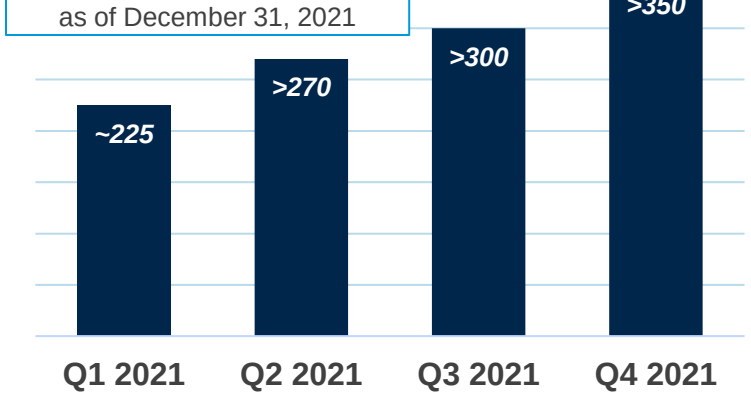


GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

~$128M
2021 revenues

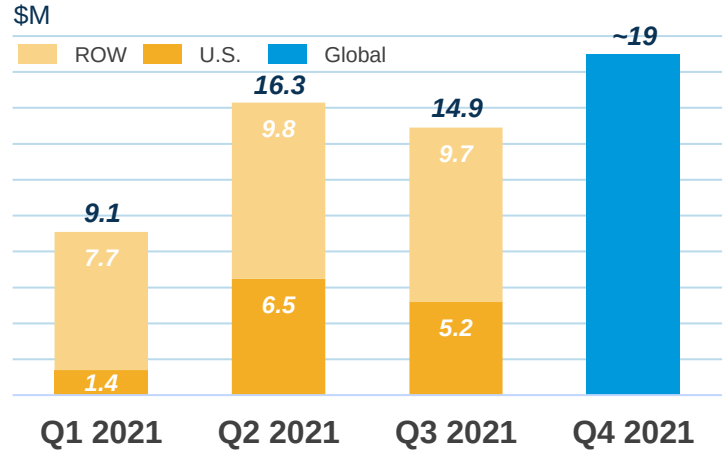


>350 patients
as of December 31, 2021

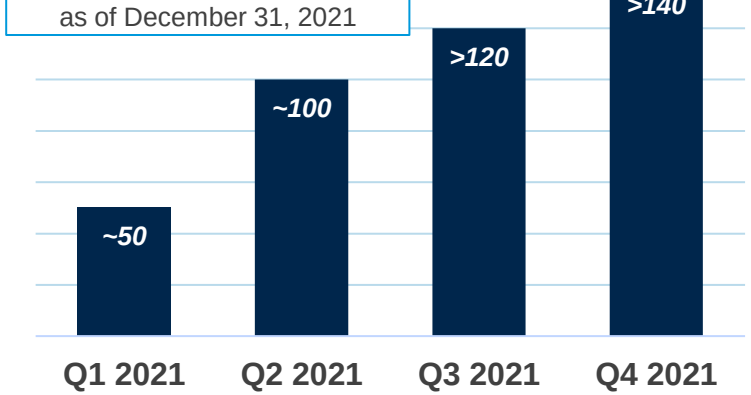


OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

~$60M
2021 revenues



>140 patients
as of December 31, 2021



* 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 2022.

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

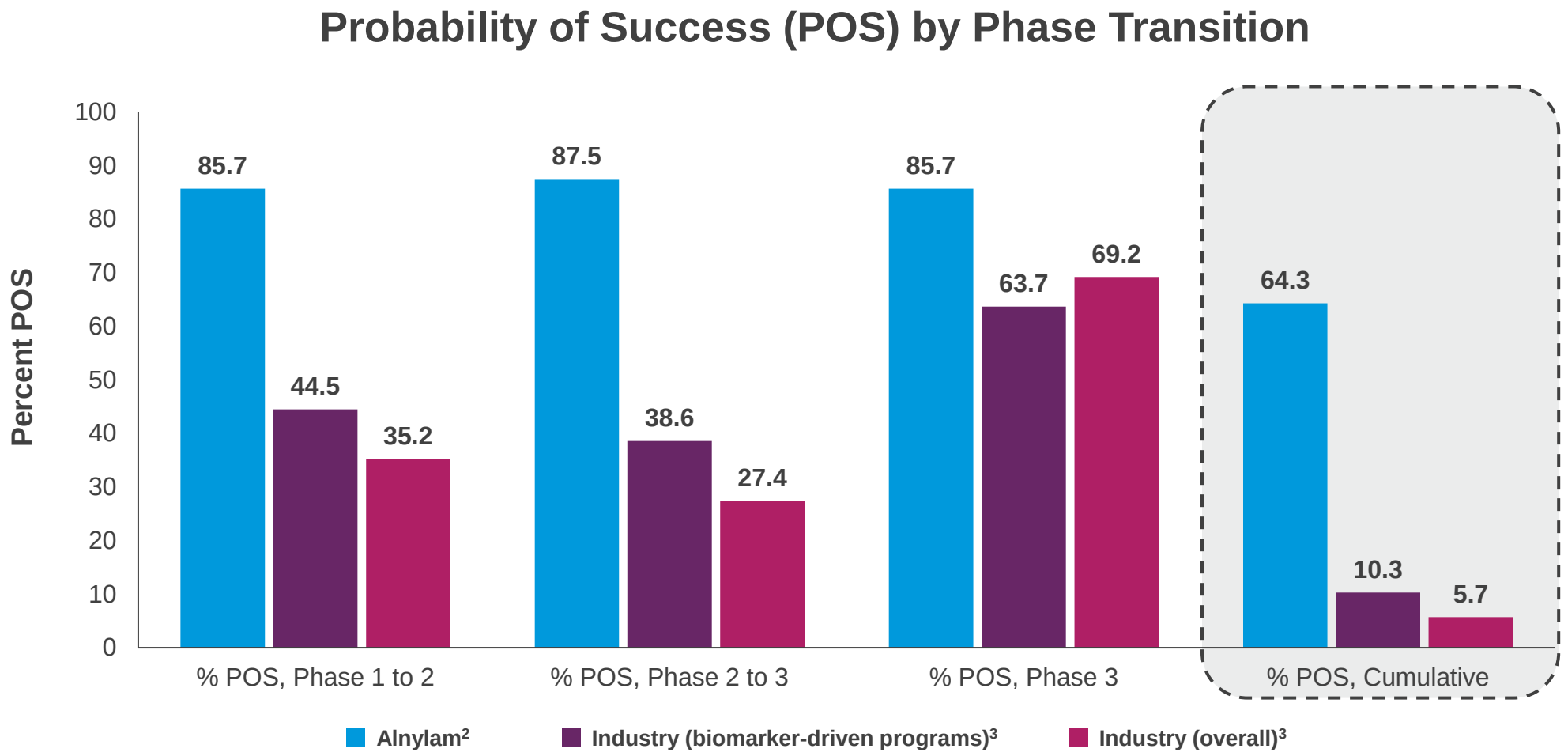
		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis-PN*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*[5]			●	Milestones & up to 20% Royalties[6]
Vutrisiran*	*hATTR Amyloidosis-PN*			●	Global
Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran*	*ATTR Amyloidosis*		●		Global
Vutrisiran[7]*	*Stargardt Disease*		○		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Renal Stones*	●		●	Global
Cemdisiran (+/- Pozelimab)[8]*	*Complement-Mediated Diseases*		●		50-50; Milestone/Royalty
Belcesiran[9]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[10]*	*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] Phase 3 study of vutrisiran in Stargardt Disease expected to initiate in late 2022; [8] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [9] Dicerna is leading and funding development of belcesiran; [10] 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 January 2022

High-Yield Productivity of Alnylam RNAi Therapeutics Platform

Comparison of Historical Industry Metrics to Alnylam Portfolio[1]



[1] Analysis as of November 2021; 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	January 21, 2022 Société Francophone du Nerf Périphérique
Potential FDA Approval of Vutrisiran	Early 2022 *(PDUFA date April 14, 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
KARDIA-1 Phase 2 Topline Results with Zilebesiran	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

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

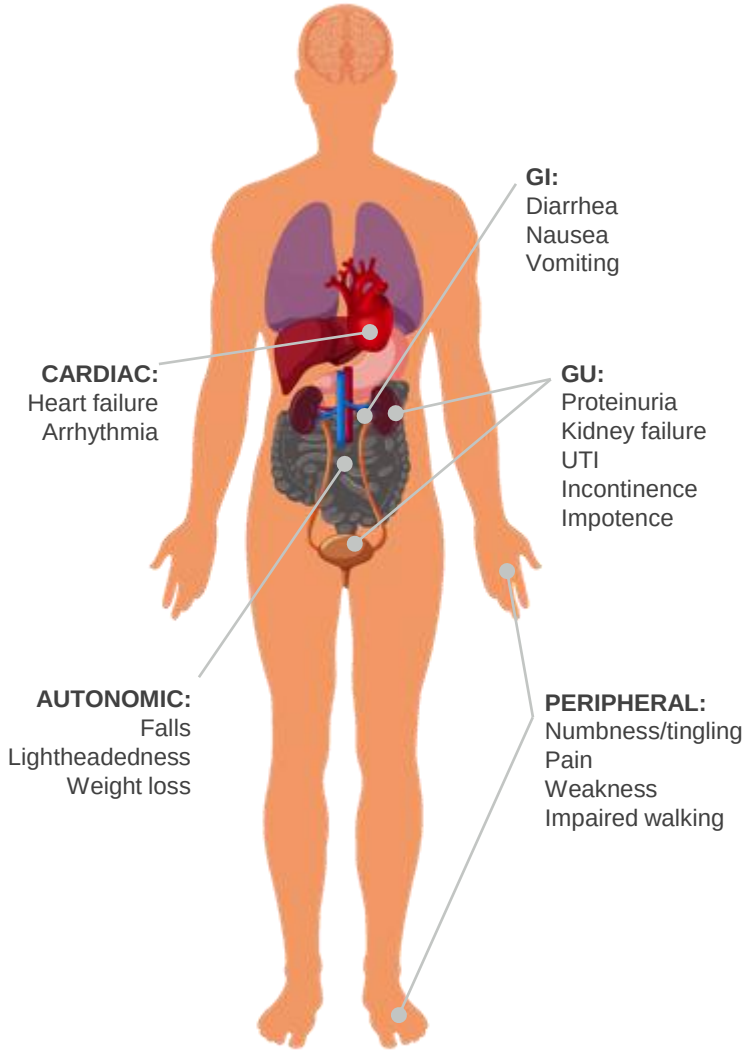
~50,000

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

Patisiran APOLLO-B
ATTR Amyloidosis with CM (incl. WT)‡

Vutrisiran ***Biannual Dosing Regimen***
hATTR Amyloidosis with PN & Mixed†

Vutrisiran HELIOS-A
hATTR Amyloidosis with PN & Mixed†

onpattro (patisiran) APOLLO
*hATTR Amyloidosis with PN & Mixed**

2022 – 2024

Novel siRNA Conjugates^
Ocular & CNS hATTR Amyloidosis

ALN-TTRsc04
ATTR Amyloidosis

Vutrisiran HELIOS-C
Early ATTR Amyloidosis†

Vutrisiran **Phase 3**
Stargardt Disease

Vutrisiran HELIOS-B
ATTR Amyloidosis with CM (incl. WT)†

Patisiran APOLLO-B
ATTR Amyloidosis with CM (incl. WT)‡

Vutrisiran HELIOS-A
hATTR Amyloidosis with PN & Mixed†

onpattro (patisiran) 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 has 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

† Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; additional studies and future development possible; ^ 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

TTR Franchise Phase 3 Program

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

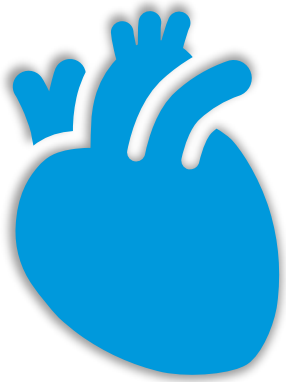
APOLLO-B

patisiran

N = 360
hereditary & wild-type
6-minute walk test
12 months

Enrollment **complete**

Topline results expected **mid-2022**



HELIOS-B

vutrisiran

N = 655
hereditary & wild-type
mortality & cardiovascular events
30 months

Enrollment **complete**

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

Study includes optional interim analysis

Reasons for Confidence in Design and Ongoing Execution of APOLLO-B

Potential to Demonstrate Favorable Impact of Patisiran vs Placebo at 12 Months, as Measured by 6MWT

Rigorous Diagnostic Criteria for ATTR with CM

- Positive biopsy or technetium (Tc) scintigraphy with Perugini Grade 2 or 3 uptake
- Exclusion of AL amyloidosis and other causes of CM[1]
- Intraventricular septal wall thickness ≥ 12mm at baseline echo

Expertise in Study Design and Execution

- >10-year history of conducting studies in ATTR amyloidosis
- Conservatively powered; 1:1 randomization, overenrolled with 360 patients
- Rigorous approach to implementation, training, and oversight of 6MWT
- Limited number of baseline 6MWTs per patient to minimize potential training effect of repeat testing

Broad Patient Population Enrolled

- Target of ~20% hereditary / ~80% wild-type patients
- NYHA Class I, II, and III (clinical evidence of heart failure required)
- NT-proBNP >300 ng/L and <8500 ng/L[2]
- Up to 30% of patients on tafamidis at entry; all with disease progression on tafamidis
- Excludes patients who anticipate starting tafamidis w/in 12 months

Unique and Promising MOA

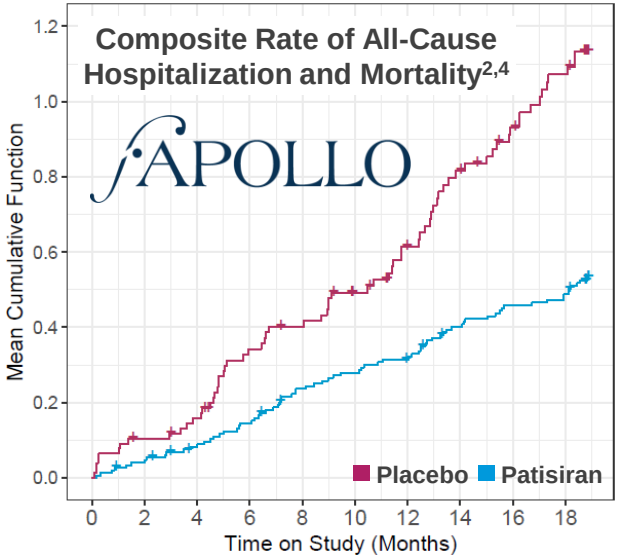
- Positive results in hATTR with PN (APOLLO and HELIOS-A), including on 10-meter walk test
- APOLLO exploratory and post-hoc analyses indicate favorable effects on echo, NT-proBNP, and hospitalization / survival[3]
- Published post-marketing case series of patisiran with evidence of reduced Tc uptake and increase in 6MWD in hATTR-CM[4]
- Encouraging HELIOS-A exploratory cardiac data, including improvement in Tc scan

Built on promising MOA of patisiran which has shown consistent exploratory data suggesting benefit in hATTR amyloidosis patients with evidence of cardiac involvement[5]

[1] Excludes other forms of cardiomyopathy (including hypertensive cardiomyopathy), marked hypertension, and other conditions that impact walking ability; [2] Screening NT-proBNP >300 ng/L and <8500 ng/L; in patients with permanent or persistent atrial fibrillation, screening NT-proBNP> 600 ng/L and <8500 ng/L; [3] Solomon S, et al. Circulation 2019; [4] Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI:10.1016/j.jcmg.2020.07.043; [5]Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for treatment of ATTR amyloidosis with CM. No conclusions can or should be drawn regarding its safety or effectiveness in treating CM in this population.

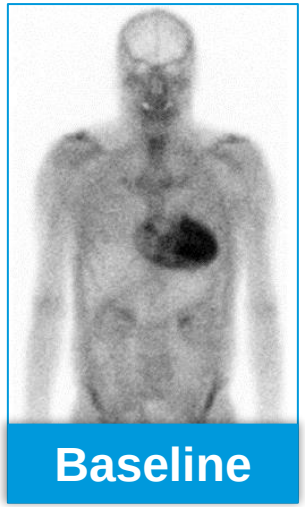
Evidence for Investigational RNAi Therapeutics in ATTR Cardiomyopathy[1]

Exploratory & Post-hoc Data from APOLLO[2]



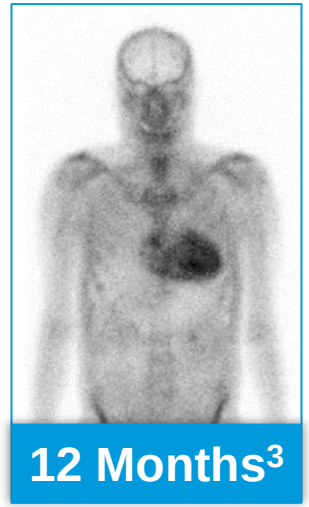
- **55%** Relative reduction in **NT-proBNP** vs. placebo[2,†]
- **0.9mm** Mean reduction in **LV wall thickness** vs. placebo[2,‡]
- **-1.4%** Improvement in **global longitudinal strain** vs. placebo[2,‡]
- **0.35m/s** Improvement in **10-MWT** vs. placebo[2,†]

Investigator-Sponsored Study from National Amyloidosis Centre, UK[3]



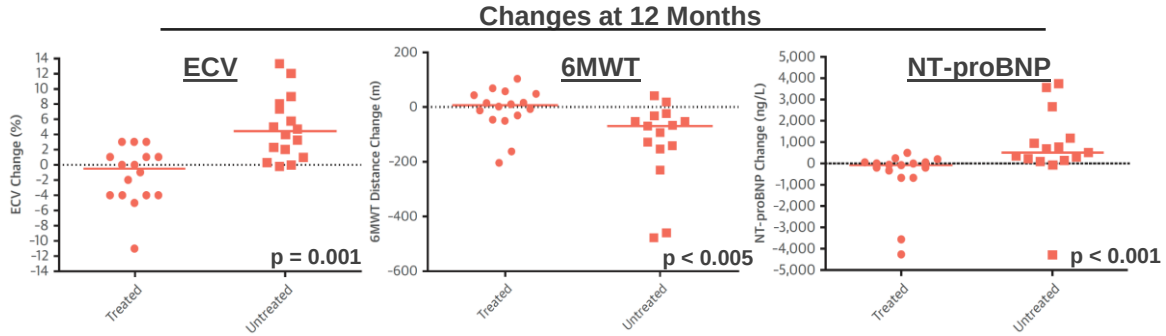
Patient with hATTR and CM, receiving patisiran and diflunisal

Example Tc-DPD Bone Scintigraphy & Image Analysis conducted as part of study, in this patient showing "unequivocal reduction in cardiac and soft tissue uptake"[3]



Cardiac Safety Data in Entire APOLLO Study Population:

	Placebo[5] (n=77)	Patisiran[5] (n=148)
Rates of Death/Hospitalization, per 100 py (95% CI)		
Death	6.2 (2.5 – 12.7)	3.2 (1.4 – 6.2)
All-cause hospitalization	69.7 (54.3 – 87.7)	32.9 (25.9 – 41.1)
Cardiac hospitalization	15.6 (9.0 – 24.9)	8.2 (5.0 – 12.6)
Hospitalization and/or death	71.8 (56.1 – 90.1)	34.7 (27.5 – 43.1)
Cardiac hospitalization and/or death	18.7 (11.4 – 28.8)	10.1 (6.4 – 14.9)



[1] Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for treatment of cardiac amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in treating CM in this population; [2] Solomon S, et al. Circulation 2018;

[3] Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI:10.1016/j.jcmg.2020.07.043; [4] Analysis of hospitalization/death data was conducted post-hoc based on data collected from AE CRFs; hospitalization/death events caused by SAEs within 28 days of last dose of study drug were included; hospitalization events caused by SAEs within SOC of cardiac disorder were classified as cardiac hospitalization; [5] For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio (HR) 0.48 [0.34, 0.69]; † nominal p<0.01; ‡ nominal p<0.05

Stargardt Disease

Promising New Opportunity for Vutrisiran

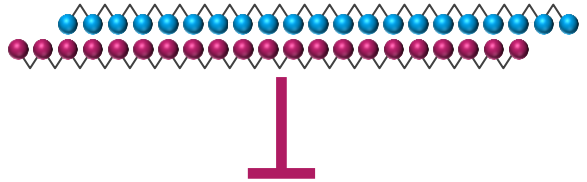
Description

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-PN[1]
GIVLAARI
OXLUMO: PH1
Vutrisiran: hATTR-PN[3]
Fitusiran
Belcesiran
ALN-HTT

SPECIALTY

Patisiran: ATTR-CM[2]
Vutrisiran: ATTR-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] Patisiran has 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; [3] Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; NDA accepted seeking approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis in adults based on positive 9-Month results in HELIOS-A study; HELIOS-B study of vutrisiran in ATTR patients with cardiomyopathy is ongoing; [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.

Commercial Capabilities Support Potential Expansion to Prevalent Diseases

Sophisticated, Scalable, and Global Medical and Commercial Organizations

Scalable Capabilities

RARE

ONPATTRO: hATTR-PN[1]
GIVLAARI
OXLUMO: PH1
Vutrisiran: hATTR-PN[3]
Fitusiran
Belcesiran
ALN-HTT

SPECIALTY

Patisiran: ATTR-CM[2]
Vutrisiran: ATTR-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

Patient Support: Experienced patient support systems enable >90% adherence — Alnylam ASSIST™

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 — Harvard Pilgrim Health Care

Diagnosis: Sophisticated and digitally enabled patient- and HCP-finding capabilities — AlnylamAct™

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] Patisiran has 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; [3] Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; NDA accepted seeking approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis in adults based on positive 9-Month results in HELIOS-A study; HELIOS-B study of vutrisiran in ATTR patients with cardiomyopathy is ongoing; [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 therapy targeting PCSK9 with up to 52% reduction in LDL cholesterol
- Potential to reduce ASCVD risk at population level

PHASE 2

Zilebesiran

Hypertension

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

ALN-HBV02 (VIR-2218)

Chronic Hepatitis B Virus (HBV) Infection

- Targets conserved region in X gene, resulting in multi-log reductions in HBsAg levels
- 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
- Demonstrated reductions in kidney stone event rate and nephrocalcinosis in PH1

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

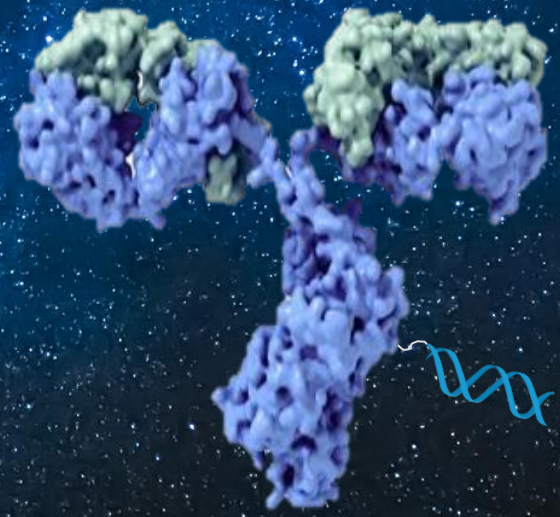
Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; Vir is leading and funding development of ALN-HBV02; With the exception of Leqvio® (inclisiran), these are investigational agents and have not been approved by the FDA, EMA, or any other regulatory agency and no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

Multiple Drivers of Future Growth

TTR Franchise Leadership

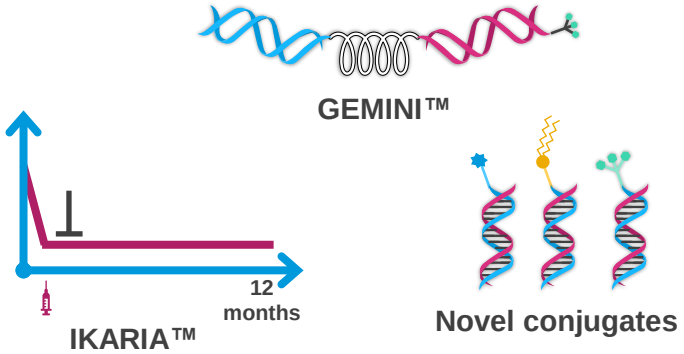
Expansion into Prevalent Diseases

Engine for Sustainable Innovation



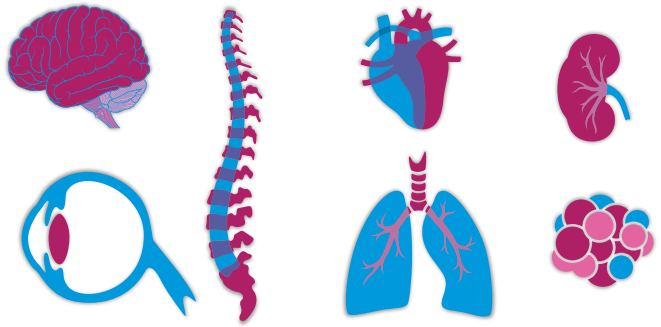
Sources of Sustainable Innovation

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, Gene X, and more)

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

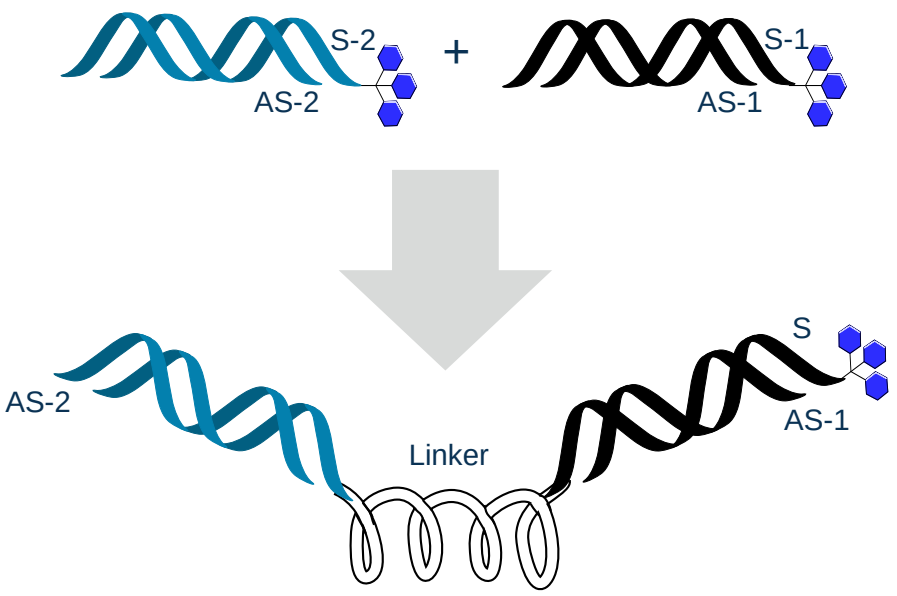
GEMINI

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)
- Could potentially 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
- 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

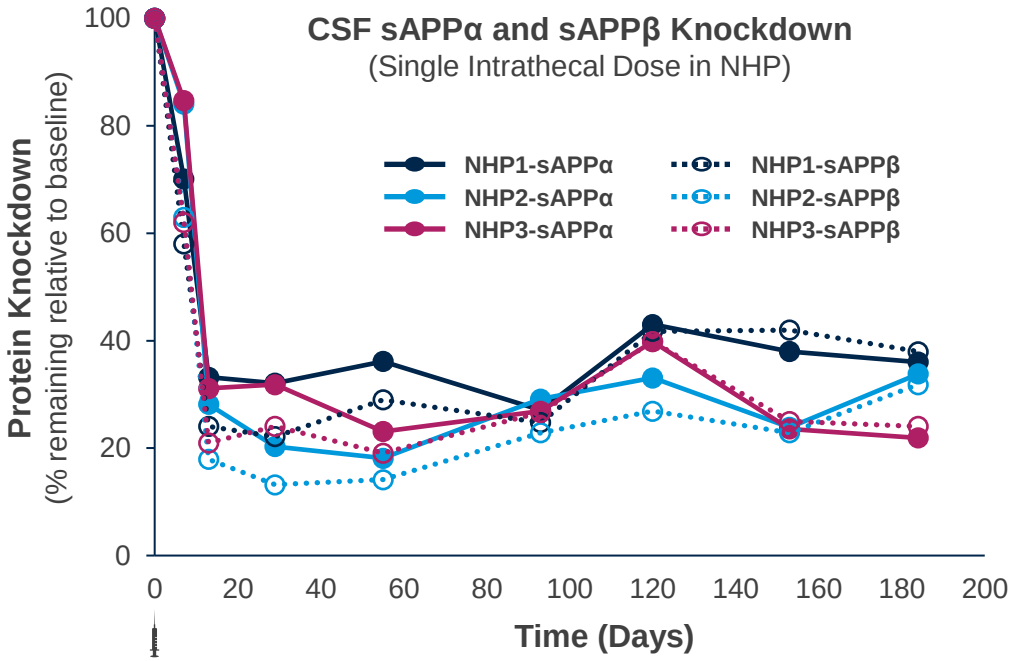
- Mutations and duplications in *APP* gene cause Alzheimer's disease (AD), cerebral amyloid angiopathy (CAA), or both
- Mutations that reduce production of APP cleavage products are protective against AD
- AD (most common cause of dementia) and CAA (second most common cause of intracerebral hemorrhage)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

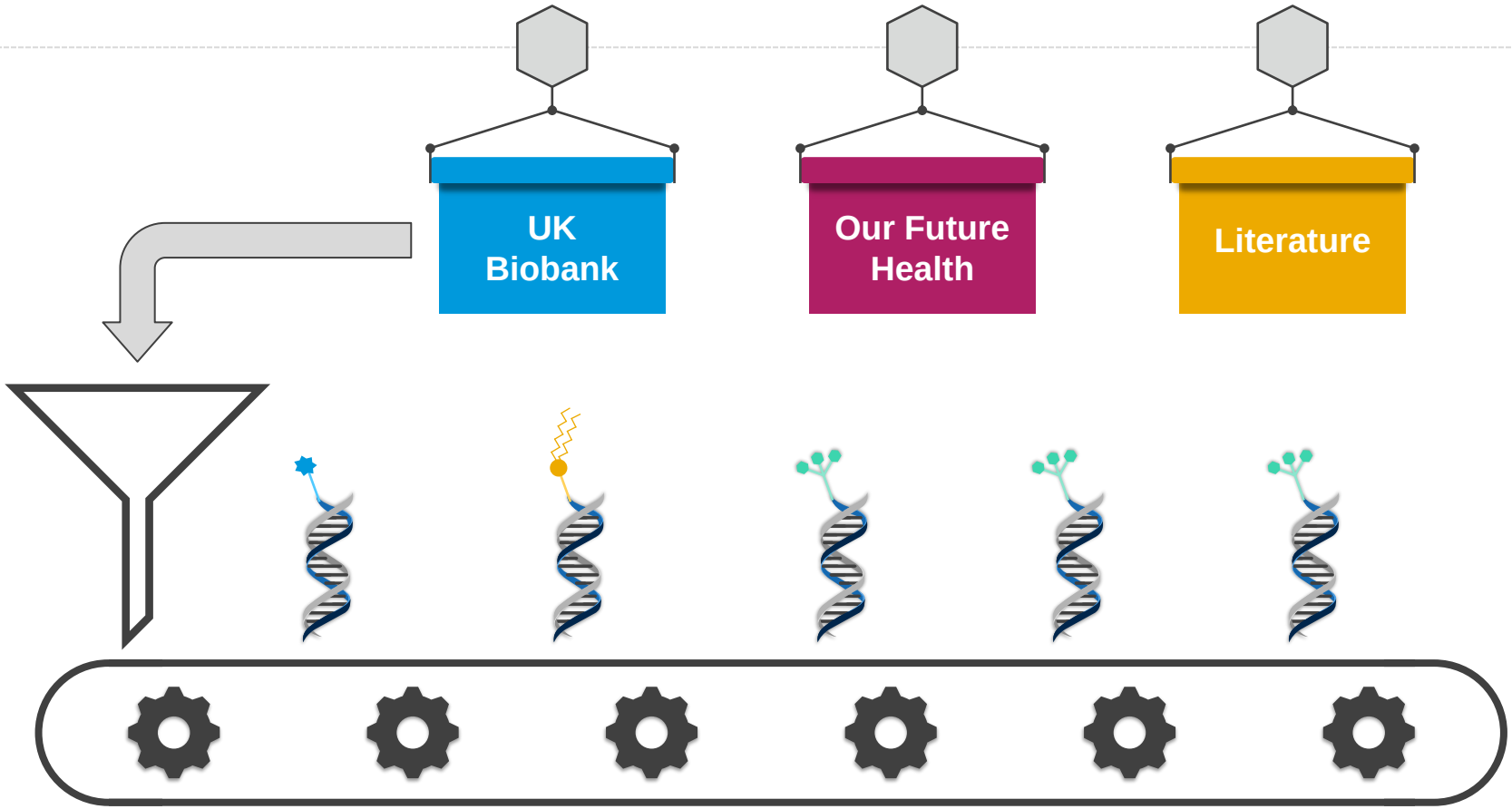
- Phase 1 planned to initiate in early-onset AD patients in early 2022 with initial human data expected at or around year-end 2022



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)		*Combined Net Product Revenue Guidance to be Provided at Q4'21 Earnings*			●
PATISIRAN	hATTR/ATTR Amyloidosis	APOLLO-B Phase 3 Topline Results		●	
		File sNDA for ATTR-CM			●
VUTRISIRAN*	hATTR/ATTR Amyloidosis	FDA Approval (4/14/22 PDUFA)	●		
		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-1 Enrollment		●	
		Complete KARDIA-2 Enrollment			●
		KARDIA-1 Phase 2 Topline Results			●
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

Alnylam 2022 Goals

			Early	Mid	Late
onpattro (patisiran) / GIVLAARI (givosiran) / OXLUMO (lumasiran)		*Combined Net Product Revenue Guidance to be Provided at Q4'21 Earnings*			●
PATISIRAN	hATTR/ATTR Amyloidosis	APOLLO-B Phase 3 Topline Results		●	
		File sNDA for ATTR-CM			●
VUTRISIRA		FDA Approval (4/14/22 PDUFA)	●		
					●
					●
ALN-TTRsc					●
					●
LUMASIRA					●
INCLISIRA					
CEMDISIRA (+/- POZELIM					
ZILEBESIRA					●
					●
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	●	●	●

- 5 commercial products
- 1 product launch
- 1 Phase 3 readout
- 1 sNDA filing
- 5 Phase 3 programs
- 5 Phase 2 programs
- 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

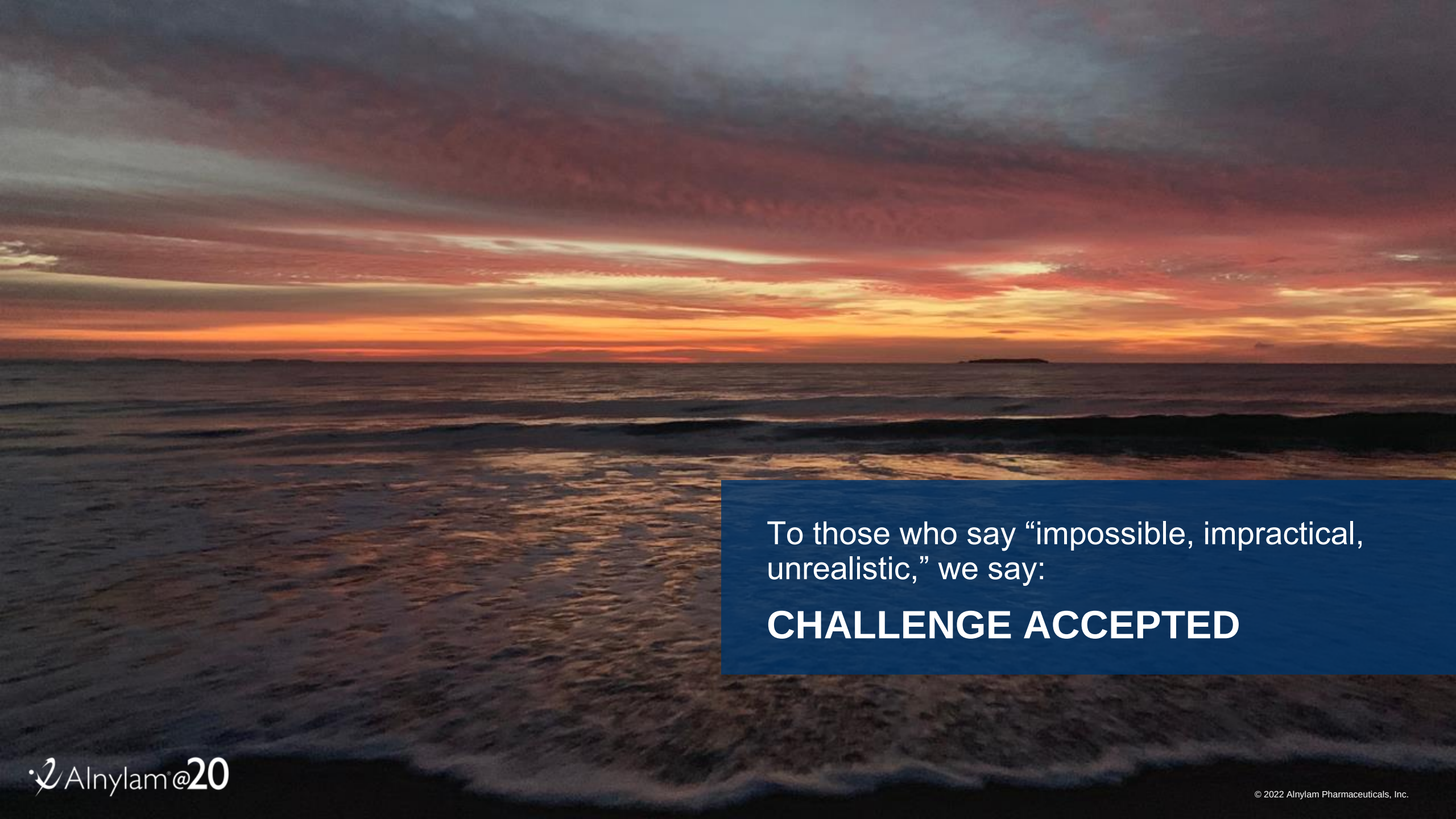
- Commitment to People
- Scientific Innovation
- Diversity, Equity, & Inclusion
- Social Responsibility

The Boston Globe TOP PLACES TO WORK 2015-2021

Science 2021 TOP EMPLOYER

FAST COMPANY BEST WORKPLACES FOR INNOVATORS 2021

Bloomberg Gender-Equality Index 2021



Alnylam@20