Nathan (USA)
Diagnosed with AHP

Third Quarter 2022 Financial Results

October 27, 2022

Alnylam®@20

Agenda

Welcome

- Christine Lindenboom
  Senior Vice President, Investor Relations & Corporate Communications

Overview

- Yvonne Greenstreet, MBChB, MBA
  Chief Executive Officer

Commercial Highlights

- Tolga Tanguler
  Chief Commercial Officer

Alnylam Pipeline

- Akshay Vaishnaw, M.D., Ph.D.
  President

Financial Summary and Upcoming Milestones

- Jeff Poulton
  Chief Financial Officer

Q&A Session

Alnylam Forward Looking Statements & Non-GAAP Financial Measures

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, the drivers of our future growth potential, including the potential of our TTR franchise, the potential submission of an sNDA for ONPATTRO for patients with ATTR amyloidosis with cardiomyopathy by year-end for FDA review, the potential expansion of Alnylam's TTR franchise, assuming successful review and approval of the ONPATTRO sNDA, the achievement of additional pipeline milestones and data, including relating to ongoing clinical studies of vutrisiran, zilebesiran, lumasiran, cemdisiran, ALN-HBV02 (Vir 2218), ALN-APP and ALN-XDH, and the filing of an IND for ALN-TTRsc04, the expected range of net product revenues for 2022, the updated expected range of net revenues from collaborations and royalties for 2022, the expected range of aggregate annual GAAP and non-GAAP R&D and SG&A expenses for 2022, and the potential impact of foreign exchange rates on our results, growth rates and 2022 guidance. 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 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 patisiran and vutrisiran; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including 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 or 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; the impact of foreign exchange rates on our results; 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.

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. The items included in GAAP presentations but excluded for purposes of determining non-GAAP financial measures for the periods referenced herein are stock-based compensation expenses, realized and unrealized (gains) losses on marketable equity securities and loss on the extinguishment of debt. We have excluded the impact of stock-based compensation expense, which may fluctuate from period to period based on factors including the variability associated with performance-based grants for stock options and restricted stock units and changes in our stock price, which impacts the fair value of these awards. We have excluded the impact of the realized and unrealized (gains) losses on marketable equity securities because we do not believe these adjustments accurately reflect the performance of our ongoing operations for the period in which such gains or losses are reported, as their sole purpose is to adjust amounts on the balance sheet. We excluded the loss on the extinguishment of debt because we believe the item is a non-recurring transaction outside the ordinary course of our business.

Percentage changes in revenue growth at Constant Exchange Rates, or CER, are presented excluding the impact of changes in foreign currency exchange rates for investors to understand the underlying business performance. The current period's foreign currency revenue values are converted into U.S. dollars using the average exchange rates from the prior period.

Yvonne Greenstreet, MBChB, MBA

Chief Executive Officer

Overview

Multiple Drivers of Future Growth

TTR Franchise Leadership

Expansion into Prevalent Diseases

Engine for Sustainable Innovation

Andreas (Sweden)
Diagnosed with hATTR amyloidosis

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

Tolga Tanguler

Chief Commercial Officer

Commercial Highlights

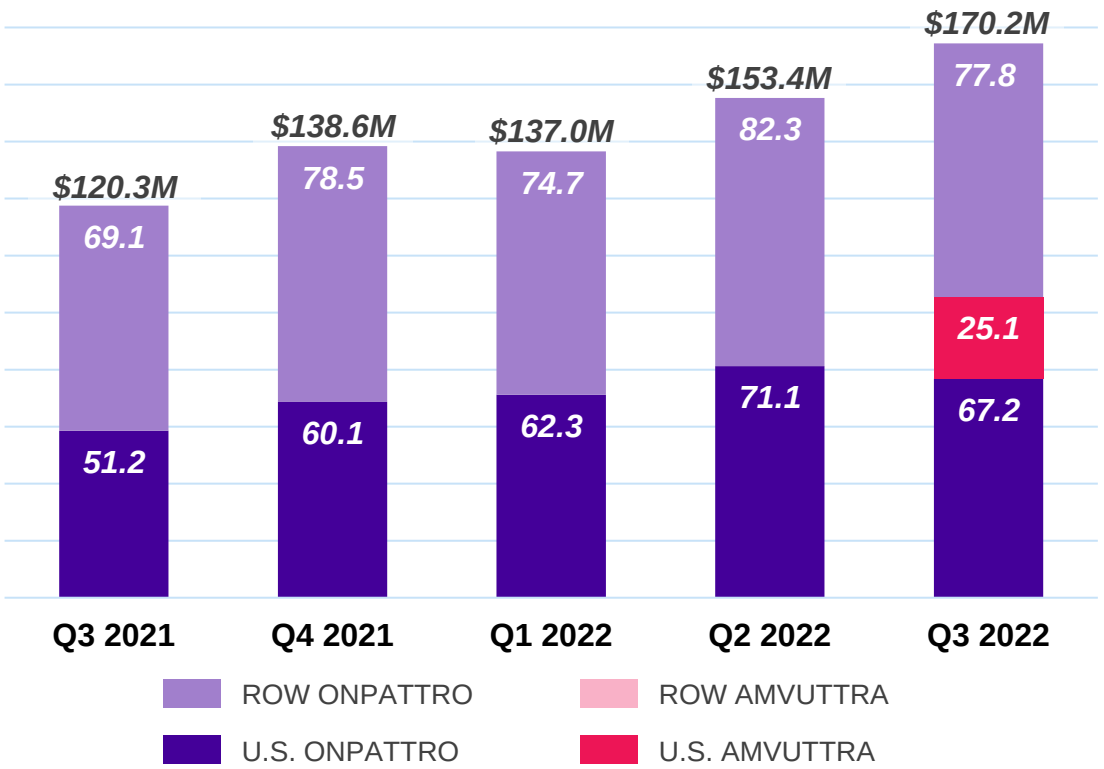
TTR Franchise Update: Q3 2022

$170M

ONPATTRO ($145M) and AMVUTTRA ($25M) Global Q3 2022 Net Product Revenues

>2,580

Patients Worldwide on Commercial ONPATTRO (~2,400) and AMVUTTRA (~180) at end of Q3 2022



Q3 TTR Franchise Highlights

	YoY % Growth	QoQ % Growth
U.S.	80%	30%
ROW	13%	-5%
Global	41%	11%

- U.S. TTR franchise QoQ growth of 30% impacted by:
  - Demand growth +19% driven by strong AMVUTTRA launch uptake more than offsetting decrease in ONPATTRO demand
  - Inventory dynamics +11% primarily due to initial AMVUTTRA launch stocking
- ROW QoQ growth of -5% primarily due to increase in patient demand more than offset by timing of orders in partner markets and Fx headwinds
- Strengthening USD continues to create Fx headwind for ROW markets (YoY Global CER[1] growth = 52%)

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

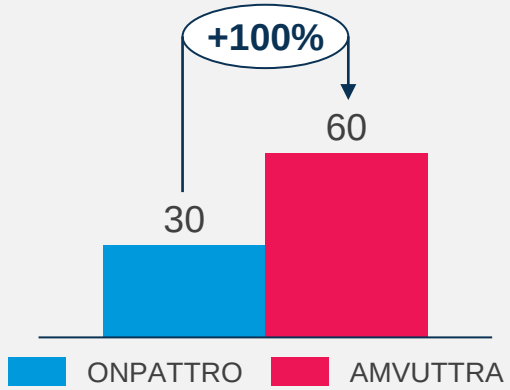
amvuttra™ (vutrisiran) injection 25 mg/0.5 mL

[1] CER = constant exchange rate, representing growth calculated as if exchange rates had remained unchanged from those used in Q3 2021.

AMVUTTRA® (vutrisiran) Update: Q3 2022

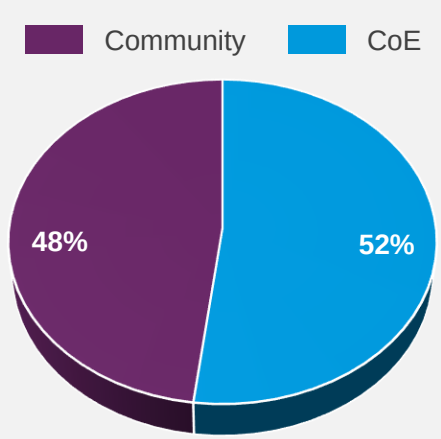
Encouraging Early Launch Performance Following U.S. Approval on June 13th

Doubled "New Start Form" Monthly Average Since Launch



- ~180 patients started treatment
- 475 Start Forms received from launch through September 30, 2022*
- ~46% of Start Forms from new patients

Balanced Growth Across Account Types



- ~17% of Start Forms sourced from new prescribers

Broad Patient Base and Encouraging Access Trends

- Patient types:
  - Newly diagnosed
  - Diagnosed, not treated before
  - Switched from ONPATTRO and other therapies
  - Discontinued ONPATTRO and restarted on AMVUTTRA (small number)
- No significant access headwinds
- J-Code on track for January 1, 2023
- Average time from Start Form to treatment in line with ONPATTRO benchmark

* Start Forms are an incomplete picture of U.S. demand

AMVUTTRA and ONPATTRO are approved in the U.S. for the PN of hATTR amyloidosis in adults, and in the EU and Japan for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy

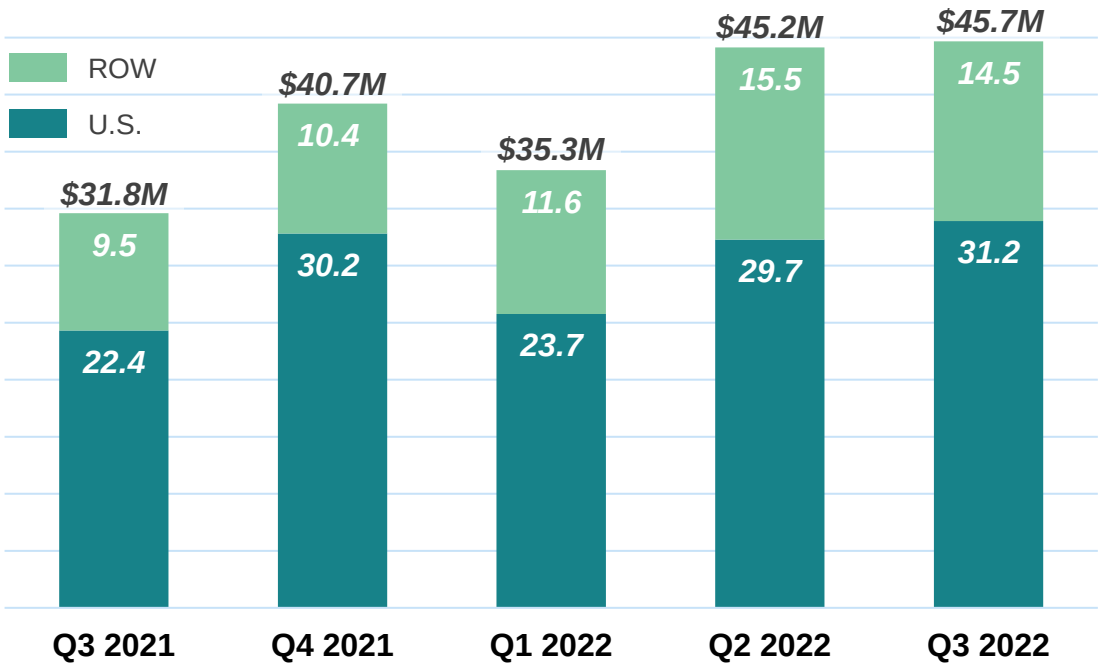
GIVLAARI® (givosiran) Update: Q3 2022

$46M

GIVLAARI Global Q3 2022 Net Product Revenues

>460

Patients Worldwide on Commercial GIVLAARI at end of Q3 2022



Q3 Highlights

	YoY % Growth	QoQ % Growth
U.S.	39%	5%
ROW	53%	-6%
Global	43%	1%

- U.S. QoQ growth of 5% impacted by:
  - Demand growth of +7% driven by an increase in patients on therapy
  - Modest changes in inventory stocking and gross to net sales deductions slightly offset increase in patient demand (-2%)
- ROW QoQ growth of -6% due primarily to increase in patient demand more than offset by lower net pricing and Fx headwinds
- Strengthening USD continues to create Fx headwind for ROW markets (YoY Global CER[1] growth = 50%)

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

GIVLAARI is approved in the U.S. and Japan for the treatment of adults with acute hepatic porphyria, and in the EU for the treatment acute hepatic porphyria in adults and adolescents aged 12 and above.

[1] CER = constant exchange rate, representing growth calculated as if exchange rates had remained unchanged from those used in Q3 2021.

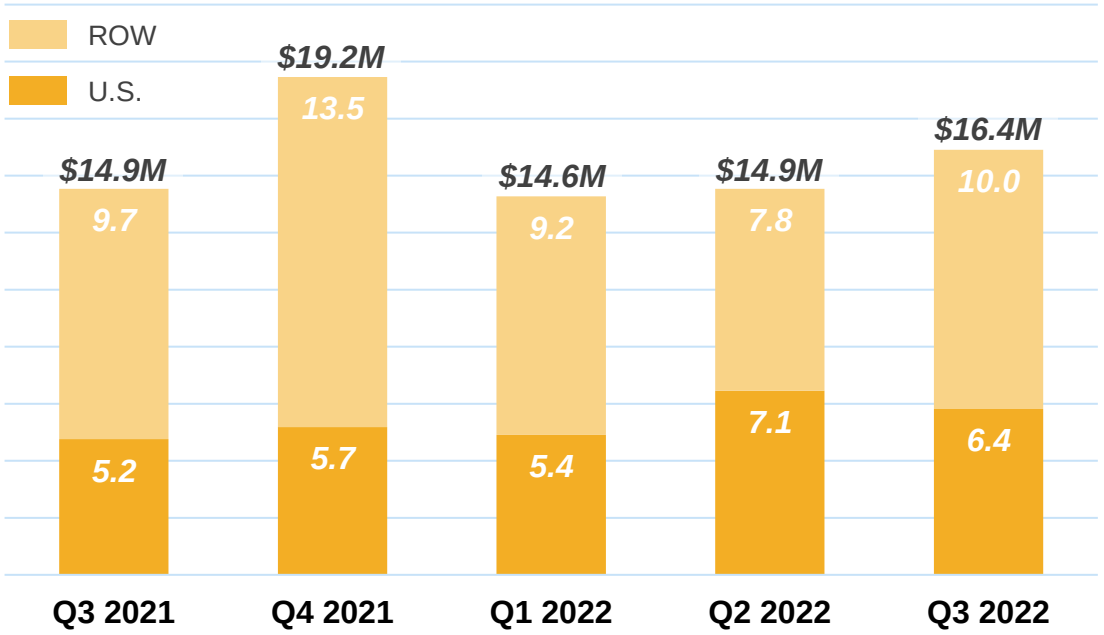
OXLUMO® (lumasiran) Update: Q3 2022

$16M

OXLUMO Global Q3 2022 Net Product Revenues

>230

Patients Worldwide on Commercial OXLUMO at end of Q3 2022



Q3 Highlights

	YoY % Growth	QoQ % Growth
U.S.	22%	-10%
ROW	4%	29%
Global	10%	10%

- U.S. QoQ growth of -10% impacted by:
  - Demand growth of -1% driven by an increase in patients on therapy offset by fewer patients on monthly loading dose
  - Reduction of inventory in the distribution channel during Q3
- ROW QoQ growth of 29% driven by increase in patients on therapy and higher net realized price offset by Fx headwinds
- Strengthening USD continues to create Fx headwind for ROW markets (YoY Global CER[1] growth = 20%)

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

OXLUMO is approved in the U.S. for the treatment of primary hyperoxaluria type 1 to lower urinary and plasma oxalate levels in pediatric and adult patients and in the EU for the treatment of primary hyperoxaluria type 1 in all age groups.

[1] CER = constant exchange rate, representing growth calculated as if exchange rates had remained unchanged from those used in Q3 2021.

Akshay Vaishnaw, M.D., Ph.D.
President

Alnylam Pipeline

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 and HFSA – Sept 2022

sNDA submission 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

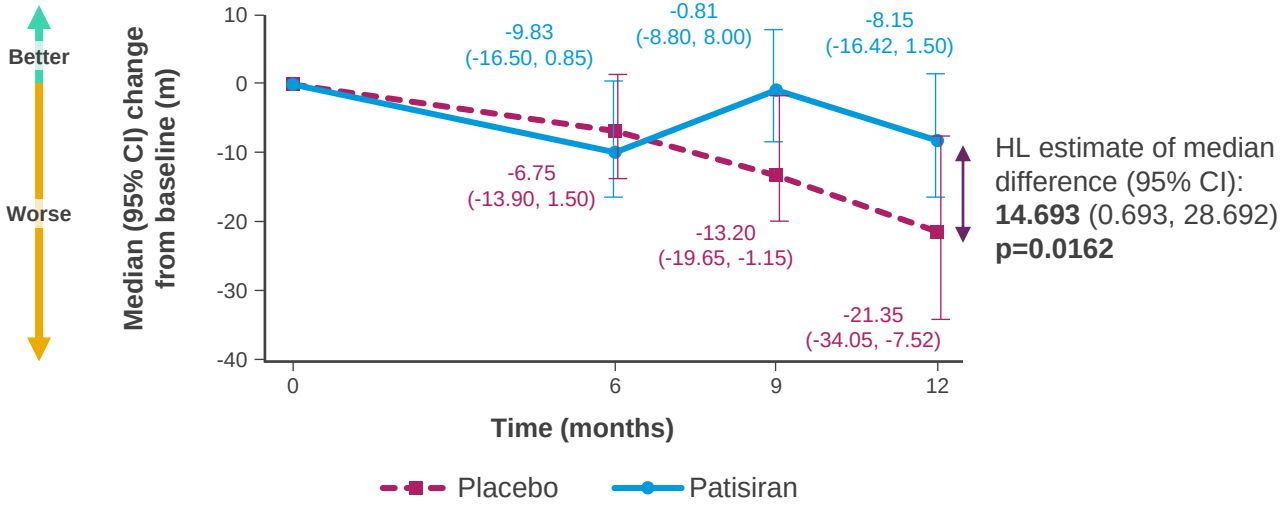
* Composite all-cause mortality, frequency of CV events, and change from baseline in 6-MWT; Composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in patients not on tafamidis at baseline; Composite all-cause mortality, frequency of all-cause hospitalizations and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

APOLLO-B Phase 3 Study Results

Primary and First Secondary Endpoints

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

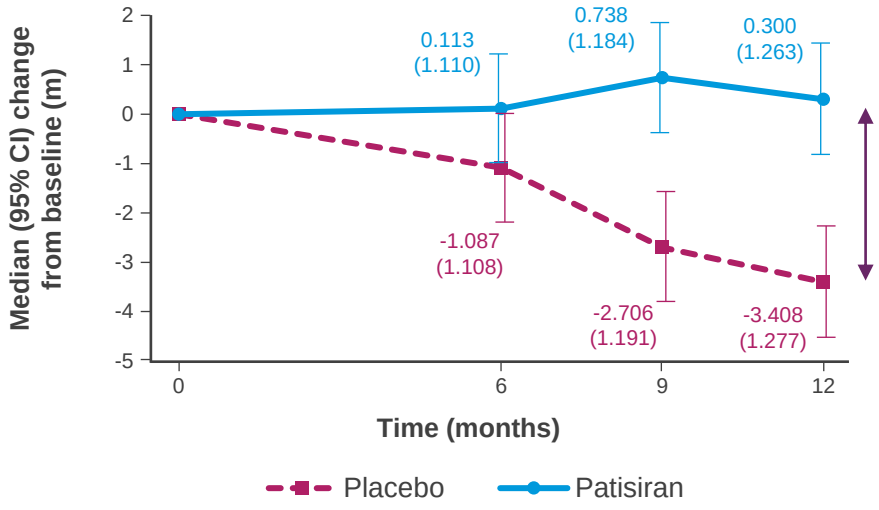
Change from Baseline in 6-MWT[a]



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·A Phase 3 Study

Randomized, Open-Label Study in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy

HELIOS·A

- As previously reported, the primary endpoint of change from baseline in mNIS+7 at Month 9 was met[1]

Patient Population
N=164

- 18–85 years old
- hATTR amyloidosis with polyneuropathy; any *TTR* mutation
- NIS 5–130 and PND ≤IIIB
- KPS ≥60%
- Prior tetramer stabilizer use permitted

3:1 RANDOMIZATION

Stratification:
TTR V30M vs non-V30M
Baseline NIS <50 vs ≥50

n=122

Vutrisiran
25 mg
SC Q3M

or

n=42

Reference comparator
(patisiran)
0.3 mg/kg
IV Q3W

Efficacy Assessments

Vutrisiran vs APOLLO Placebo

Primary Endpoint (at Month 9; previously presented[1])
- Change from baseline in mNIS+7[a]

Secondary Endpoints
Change from baseline in:
- mNIS+7 at Month 18
- Norfolk QOL-DN[b] at Months 9 and 18
- 10-MWT[c] at Months 9 and 18
- mBMI[d] at Month 18
- R-ODS[e] at Month 18

Selected Exploratory Endpoints
- Change from baseline in cardiac biomarkers, echocardiographic parameters to Month 18
- Change from baseline in Tc scintigraphy measures to Month 18[f]

Vutrisiran vs HELIOS-A Patisiran

Secondary Endpoint
- % serum TTR reduction to Month 18

[a]Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304). [b]Higher scores of Norfolk QOL-DN indicate worse quality of life (range, −4 to 136). [c]10-MWT speed (m/s) = 10 meters/mean time (seconds) taken to complete two assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function. [d]Lower scores of mBMI ([weight in kg/m^2] x serum albumin g/L) indicate worse nutritional status. [e]Lower scores of R-ODS indicate more disability (range, 0 to 48). [f]Tc scintigraphy was only performed at select sites, comparison to baseline, not placebo

10-MWT, 10-meter walk test; ATTRv, transthyretin-mediated amyloidosis (v for variant); hATTR, hereditary transthyretin-mediated amyloidosis; IV, intravenous; KPS, Karnofsky performance status; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; Tc, technetium; TTR, transthyretin.

1. Adams D et al. *Neurology* 2021;96(15 Supplement):1234.

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

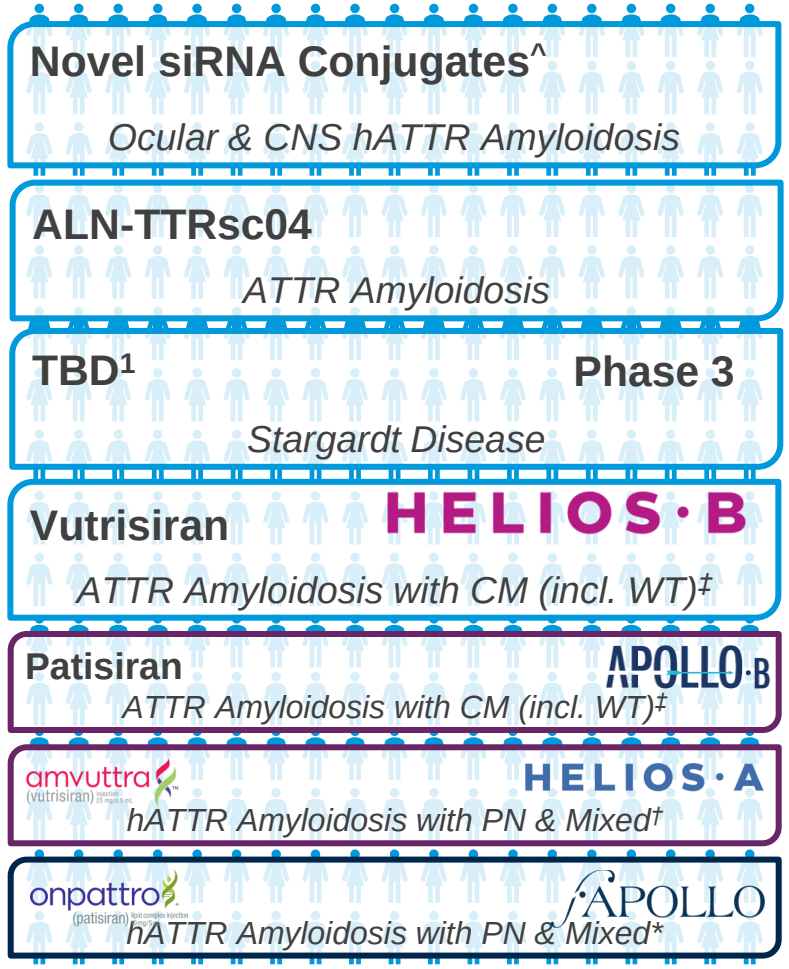
Topline results on 30-month endpoint expected **early 2024**

Alnylam TTR Franchise

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

2018 – 2022

2022 – 2024



2024 & Beyond

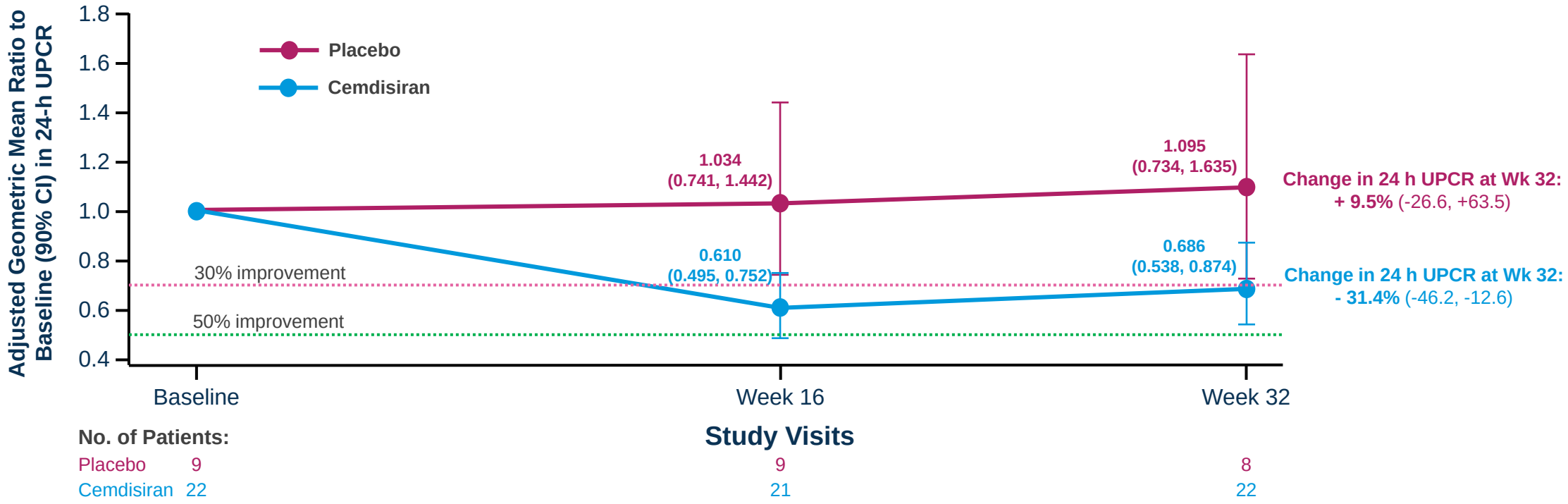
* ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; ‡ ONPATTRO and AMVUTTRA have not been approved by the FDA, EMA, or any other regulatory 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 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

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

Cemdisiran Treatment Led to Clinically Meaningful Proteinuria Reduction Compared with Placebo at Week 32

- Primary endpoint of change from baseline in 24-hour UPCR compared with placebo at Week 32 was **-37.4%** (90% CI: -61.0, 0.5)[a]
- Secondary endpoint of change from baseline in 24-hour urine total protein compared with placebo at Week 32 was **-36.2%** (90% CI: -61.6, 6.0)[a] (data not shown)



[a] Placebo-adjusted geometric mean percent change and 90% CI. A mixed-effect model repeated-measures approach was adopted, where the outcome variable was analyzed in log-scale and the model included fixed effects of treatment, scheduled visits, interaction term of treatment and scheduled visits, baseline 24-hour UPCR in log-scale, and patient as a random effect; the model-based least squares mean difference was then transformed back to the original UPCR scale. UPCR by spot urine at Week 32 was analyzed in a similar manner as appropriate. Negative numbers reflect a decrease in proteinuria. This Phase 2 study was descriptive only and did not include statistical hypothesis testing. At baseline, the mean (SD) 24-hour UPCR (g/g) values were 1.8 (1.2) in the cemdisiran group and 2.0 (0.8) in the placebo group.

CI, confidence interval; UPCR, urine protein to creatinine ratio

Cemdisiran Phase 2 IgAN Safety Summary

Double-Blind Period

- No AEs led to treatment or study discontinuation
- One death occurred in cemdisiran treatment arm due to cardiorespiratory collapse and was not considered related to study drug
  - Considered both a serious and a severe AE (see table), which occurred due to post-operative complications following bypass surgery
- Two treatment interruptions occurred in cemdisiran arm (9.1%); both were considered related to study drug
  - One patient (4.5%) had urticaria and one patient (4.5%) had an atopic dermatitis flare-up
- AEs ≥10% in cemdisiran arm included injection-site reactions (ISRs, 40.9%) and peripheral edema (13.6%)
  - Majority of ISRs were mild and transient; peripheral edema was reported as mild and not related to cemdisiran
- No safety signals regarding liver function tests[d], hematology, or renal function related to cemdisiran
- All patients required to have vaccination against meningococcal infection

Cemdisiran Phase 2 IgAN Safety Summary[a]

At least one treatment emergent adverse event, n (%)	Placebo (N=9)	Cemdisiran (N=22)
AEs	8 (88.9)	19 (86.4)
Serious AEs	0	1 (4.5)
Severe AEs	0	1 (4.5)
AEs leading to treatment interruption	1 (11.1)	2 (9.1)[b]
AEs leading to treatment discontinuation	0	0
Death[c]	0	1 (4.5)

[a] Treatment-emergent AEs includes events occurring or worsening on or after the first dose of study drug and through 28 days after the last dose or any study drug related AEs. AEs with missing causality are considered related. AEs with missing severity are considered severe. [b] Both treatment interruptions in the cemdisiran arm were transient. [c] All fatal AEs are summarized regardless of treatment-emergent classification. [d] Transient elevations in ALT and AST were observed with cemdisiran treatment, however, there were no safety concerns.

AE, adverse event; ISR, injection-site reaction.

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
TBD*	*Stargardt Disease*		○		Global
ALN-TTRsc04*	*ATTR Amyloidosis*	●			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, and in the EU and Japan for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [8] The Company is considering options for the best path forward to bring an RNAi therapeutic to patients with Stargardt Disease; [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 October 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 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
TBD*	*Stargardt Disease*		○		Global
ALN-TTRsc04*	*ATTR Amyloidosis*	●			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, and in the EU and Japan for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [8] The Company is considering options for the best path forward to bring an RNAi therapeutic to patients with Stargardt Disease; [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 October 2022

Save the date!

Alnylam®

R&D Day

December 15, 2022

A VIRTUAL EVENT

Registration information
coming soon.

Jeff Poulton

Chief Financial Officer

Financial Summary and Upcoming Milestones

Q3 2022 Financial Summary

Financial Results ($ millions)	Q3 2022	Q3 2021	Reported Growth %	CER Growth %[3]
Net Product Revenues	$232	$167	39%	49%
Net Revenues from Collaborations	$29	$20	45%	
Royalty Revenues	$3	$0		
Total Revenues	$264	$188	41%	49%
Cost of Goods Sold and Collaborations	$41	$33	26%	
Gross Margin	$223	$155	44%	
GM as % of Total Revenues[1]	*84%*	*83%*		
Non-GAAP R&D Expenses[2]	$192	$182	6%	8%
Non-GAAP SG&A Expenses[2]	$161	$121	33%	36%
Non-GAAP Operating Loss [2]	($130)	($148)	-12%	-17%

Financial Results ($ millions)	Sep 30, 2022	Dec 31, 2021
Cash & Investments[4]	$2,265	$2,436

[1] GM as a % of Total Net Product Revenues is 84.3% and 83.2% for Q3 2022 and Q3 2021, respectively (excludes $4.6M and $4.6M of Cost of Collaborations and Royalties for Q3 2022 and Q3 2021, respectively).
[2] Non-GAAP R&D expenses, non-GAAP SG&A expenses and non-GAAP operating loss exclude costs related to stock-based compensation expense.
[3] Growth rates are at Constant Exchange Rates ("CER"), CER performance is determined by comparing Q3 2022 performance (restated using Q3 2021 exchange rates) to actual Q3 2021 reported performance.
[4] Cash, cash equivalents and marketable securities.
See Appendix for a reconciliation between GAAP and non-GAAP measures

2022 Updated Full Year Guidance

	Prior FY 2022 Guidance[1]	Updated FY 2022 Guidance[2]
Net Product Revenue (ONPATTRO, GIVLAARI, OXLUMO, AMVUTTRA)	$870M – $930M	No change
Net Revenues from Collaborations & Royalties	$175M – $225M	$100M – $150M
Non-GAAP Combined R&D and SG&A Expenses[3]	$1,390M – $1,450M	No change

[1] Prior FY 2022 guidance utilized April 18, 2022 FX rates of: 1 EUR = 1.08 USD; 1 GBP = 1.31 USD; 1 CHF = 1.06 USD; 1 CAD = 0.79 USD, 1 USD = 126 JPY.
[2] Updated FY 2022 guidance utilizes September 27, 2022 FX rates of: 1 EUR = 0.96 USD; 1 GBP = 1.08 USD; 1 CHF = 1.01 USD; 1 CAD = 0.73 USD, 1 USD = 145 JPY.
[3] Primarily excludes $230-$250 million of stock-based compensation expense from estimated GAAP R&D and SG&A expenses.

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		✓	
		Submit sNDA for ATTR with cardiomyopathy			●
VUTRISIRAN*	hATTR/ATTR Amyloidosis	FDA Approval		✓	
		U.S. Launch		✓	
		EMA Approval		✓	
		Biannual Dose Regimen Data			●
ALN-TTRsc04*	ATTR Amyloidosis	File CTA			✓
		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

Q3 2022 Financial Results

Q&A Session

Q3 2022 Financial Results

Appendix

Alnylam Pharmaceuticals, Inc.

Reconciliation of Selected GAAP Measures to Non-GAAP Measures
(In thousands)

	Three Months Ended		Nine Months Ended	
	September 30, 2022	September 30, 2021	September 30, 2022	September 30, 2021
Reconciliation of GAAP to Non-GAAP research and development:				
GAAP Research and development	$ 245,371	$ 194,572	$ 620,976	$ 563,106
Less: Stock-based compensation expenses	(52,962)	(12,417)	(75,217)	(49,878)
Non-GAAP Research and development	$ 192,409	$ 182,155	$ 545,759	$ 513,228
Reconciliation of GAAP to Non-GAAP selling, general and administrative:				
GAAP Selling, general and administrative	$ 235,859	$ 142,075	$ 560,314	$ 434,257
Less: Stock-based compensation expenses	(75,156)	(20,950)	(112,665)	(71,257)
Non-GAAP Selling, general and administrative	$ 160,703	$ 121,125	$ 447,649	$ 363,000
Reconciliation of GAAP to Non-GAAP operating loss:				
GAAP Operating loss	$ (258,040)	$ (181,677)	$ (596,458)	$ (514,091)
Add: Stock-based compensation expenses	128,118	33,367	187,882	121,135
Non-GAAP Operating loss	$ (129,922)	$ (148,310)	$ (408,576)	$ (392,956)

Please note that the figures presented may not sum exactly due to rounding

Alnylam Pharmaceuticals, Inc.

Reconciliation of Revenue and Growth at Constant Currency

	September 30, 2022	
	Three Months Ended	Nine Months Ended
ONPATTRO net product revenue growth, as reported	20 %	30 %
Add: Impact of foreign currency translation	11	8
ONPATTRO net product revenue growth at constant currency	31 %	38 %
AMVUTTRA net product revenue growth, as reported	N/A	N/A
Add: Impact of foreign currency translation	N/A	N/A
AMVUTTRA net product revenue growth at constant currency	— %	— %
GIVLAARI net product revenue growth, as reported	43 %	45 %
Add: Impact of foreign currency translation	7	5
GIVLAARI net product revenue growth at constant currency	50 %	50 %
OXLUMO net product revenue growth, as reported	10 %	14 %
Add: Impact of foreign currency translation	10	7
OXLUMO net product revenue growth at constant currency	20 %	21 %
Total net product revenue growth, as reported	39 %	36 %
Add: Impact of foreign currency translation	10	8
Total net product revenue growth at constant currency	49 %	44 %

Please note that the figures presented may not sum exactly due to rounding
Constant Currency = CER