Nathan (USA)
Diagnosed with AHP

First Quarter 2023 Financial Results

May 4, 2023

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

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Alnylam Forward Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements other than historical statements of fact regarding Alnylam's expectations, beliefs, goals, plans or prospects including, without limitation, expectations regarding Alnylam's aspiration to become a leading biotech company and the planned achievement of its "*Alnylam P^{5}x25*" strategy, the potential for Alnylam to identify new potential drug development candidates and advance its research and development programs, Alnylam's ability to obtain approval for new commercial products or additional indications for its existing products, and Alnylam's projected commercial and financial performance, should be considered forward-looking statements. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on Alnylam's business, results of operations and financial condition; Alnylam's ability to successfully execute on its "*Alnylam P^{5}x25*" strategy; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for Alnylam's product candidates; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, as well as favorable pricing and reimbursement; successfully launching, marketing and selling Alnylam's approved products globally; delays, interruptions or failures in the manufacture and supply of Alnylam's product candidates or its marketed products; delays or interruptions in the supply of resources needed to advance Alnylam's research and development programs, including as may arise from the recent disruptions in the supply of non-human primates; obtaining, maintaining and protecting intellectual property; Alnylam's ability to successfully expand the indication for ONPATTRO or AMVUTTRA in the future; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations and its ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; Alnylam's ability to maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of a current government investigation and the risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with Alnylam's most recent periodic report (Quarterly Report on Form 10-Q or Annual Report on Form 10-K) filed with the SEC and in its other SEC filings. In addition, any forward-looking statements represent Alnylam's views only as of the date of this presentation and should not be relied upon as representing Alnylam's views as of any subsequent date. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

This presentation references non-GAAP financial measures. These measures are not in accordance with, or an alternative to, GAAP, and may be different from non-GAAP financial measures used by other companies. Percentage changes in revenue growth at Constant Exchange Rates, or CER, are non-GAAP financial measures which are presented excluding the impact of changes in foreign currency exchange rates for investors to understand the underlying business performance. CER represents growth calculated as if the exchange rates had remained unchanged from those used during 2022.

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Yvonne Greenstreet, MBChB, MBA

Chief Executive Officer

Overview

Multiple Drivers of Future Growth

TTR Franchise Leadership

Expansion Beyond Rare Diseases

Engine for Sustainable Innovation

Liana (Brazil)
Diagnosed with hATTR amyloidosis

Ambitious Five-Year Strategy to Drive Growth

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

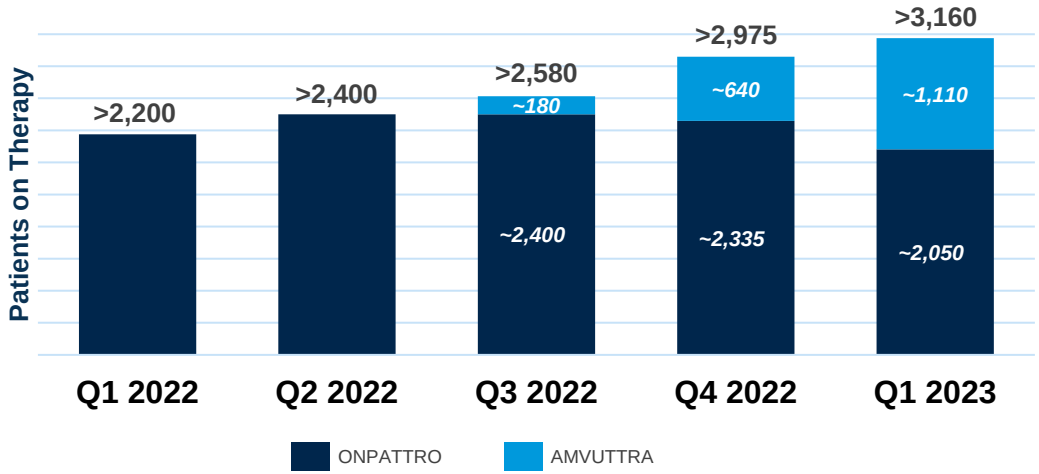
Chief Commercial Officer

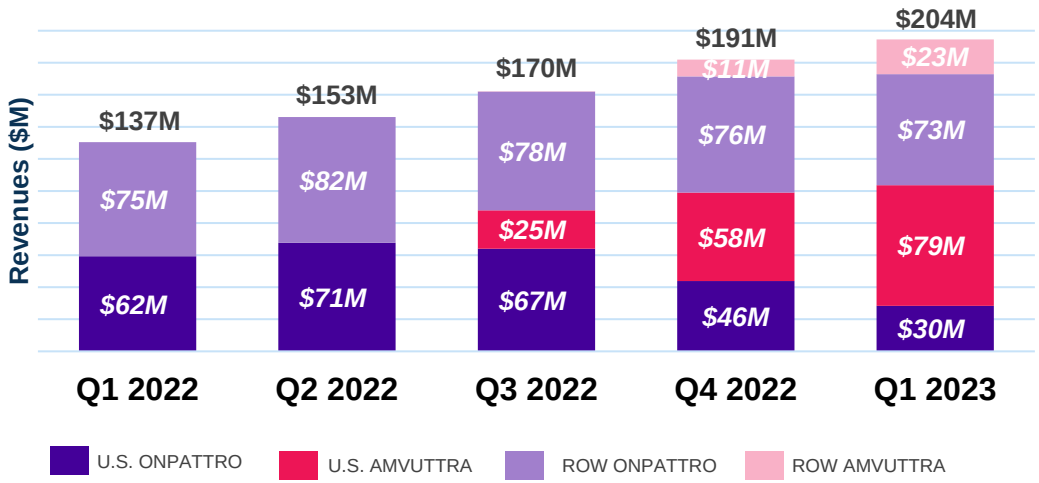
Commercial Highlights

TTR Update: Q1 2023

$204M
Total TTR
Global Q1 2023
Net Product Revenues

>3,160
Total TTR patients
worldwide at end of
Q1 2023





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

amvuttra® (vutrisiran) injection 25 mg/0.5 mL

Q1 Total TTR Highlights

	YoY % Growth	QoQ % Growth
U.S.	75%	5%
ROW	28%	9%
Global	49%	7%

- U.S. TTR QoQ growth of +5% primarily driven by:
  - Demand growth +7% due to strong AMVUTTRA demand more than offsetting decrease in ONPATTRO demand
  - Inventory dynamics -3% driven by reduction in ONPATTRO inventory in channel
- ROW QoQ growth +9% primarily due to AMVUTTRA launch demand in Japan & Germany, ONPATTRO demand in markets where AMVUTTRA not yet available, and timing of orders in partner markets
- FX headwinds continued for ROW markets (YoY Global CER[1] growth = 54%)

[1] CER = constant exchange rate, which is a non-GAAP financial measure that represents growth calculated as if exchange rates had remained unchanged from those used during 2022 – see the Financial Summary slide for more information.

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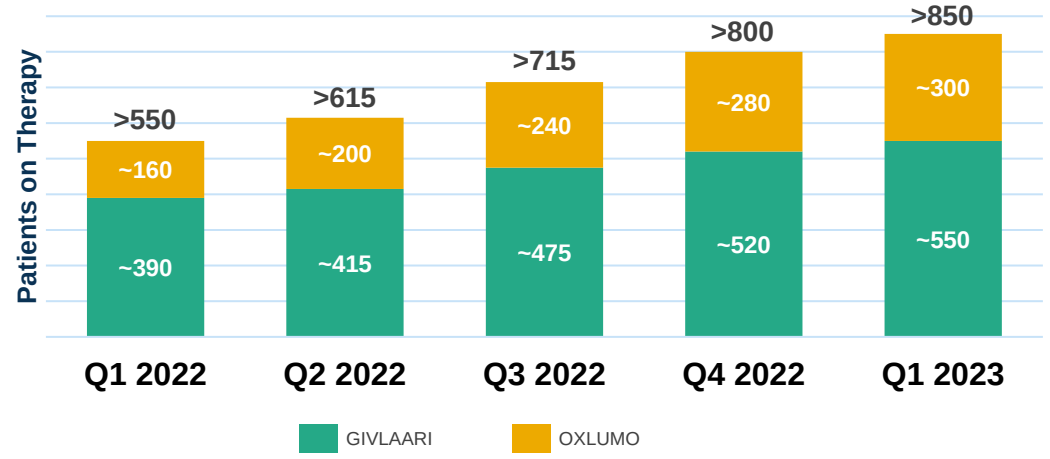
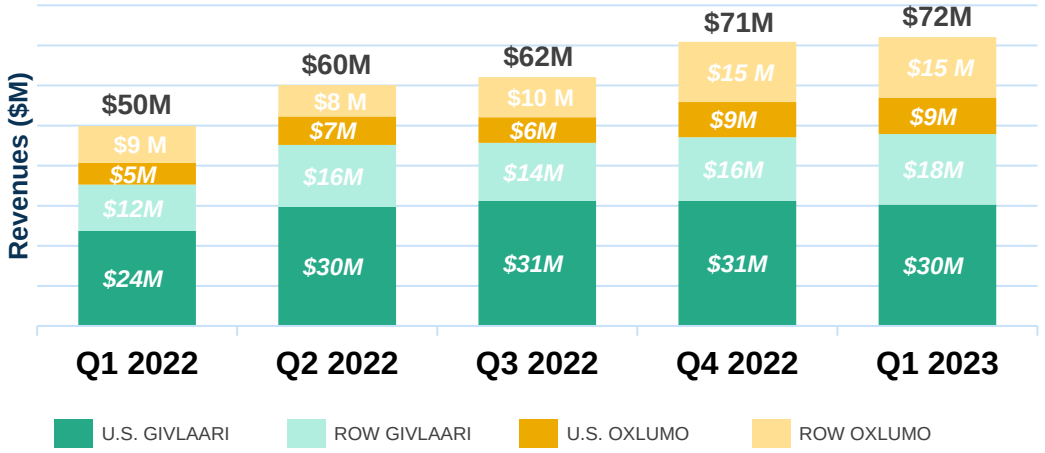
Ultra Rare Update: Q1 2023

$72M
Total Ultra Rare Global Q1 2023 Net Product Revenues

>850
Total Ultra Rare patients worldwide at end of Q1 2023





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

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

Q1 Ultra Rare Highlights

	YoY % Growth	QoQ % Growth
GIVLAARI	36%	2%
OXLUMO	66%	1%
Total Ultra Rare	45%	2%

- GIVLAARI QoQ growth +2% primarily due to:
  - US -3%: modest demand decrease primarily due to reduced patient compliance associated with seasonal impact from annual insurance reverification process
  - ROW +11%: demand increase in European markets and timing of orders in partner markets
- OXLUMO QoQ growth +1% primarily due to:
  - US +3%: modest demand increase
  - ROW (flat): driven by increase in demand across European markets offset by timing of orders in partner markets
- FX headwinds continued for ROW markets (YoY Global GIVLAARI and OXLUMO CER[1] growth = 39% & 70% respectively)

[1] CER = constant exchange rate, which is a non-GAAP financial measure that represents growth calculated as if exchange rates had remained unchanged from those used during 2022 – see the Financial Summary slide for more information.

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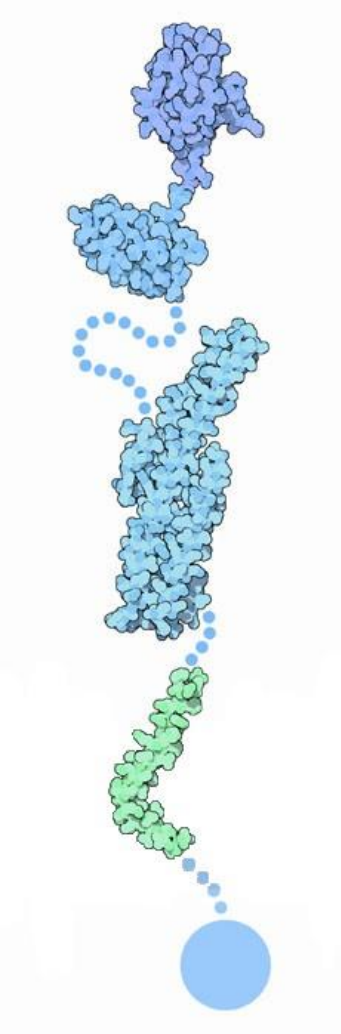
Akshay Vaishnaw, M.D., Ph.D.

President

Alnylam Pipeline

Amyloid Precursor Protein (APP)

Target for Alzheimer's Disease and Cerebral Amyloid Angiopathy



APP: One target, two distinct pathological processes

- ☑ Genetically validated target for AD and CAA
- ☑ Soluble biomarkers of target engagement (sAPPα and sAPPβ) in CSF
- ☑ Significant patient population with high unmet need in both diseases
  - AD: Over 5M people affected in U.S. (over 30M worldwide)
  - CAA: Second leading cause of intracerebral hemorrhage

Alzheimer's Disease (AD)

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

Cerebral Amyloid Angiopathy (CAA)

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

APP Protein Structure courtesy of David S. Goodsell and the RCSB Protein Data Bank

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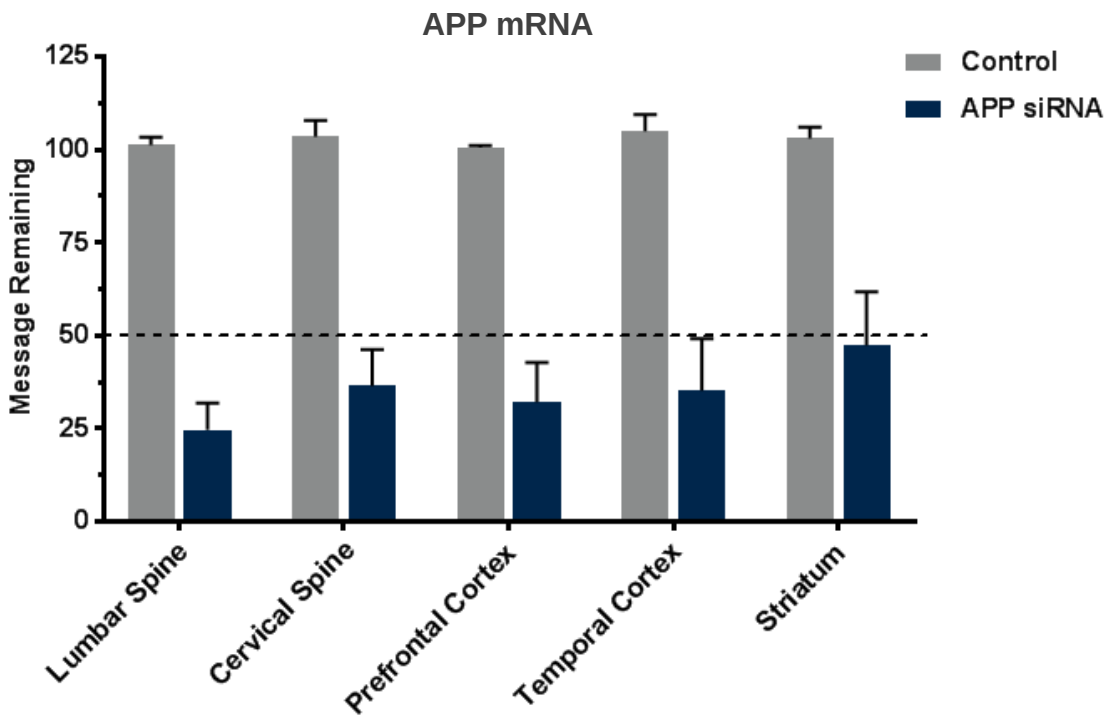
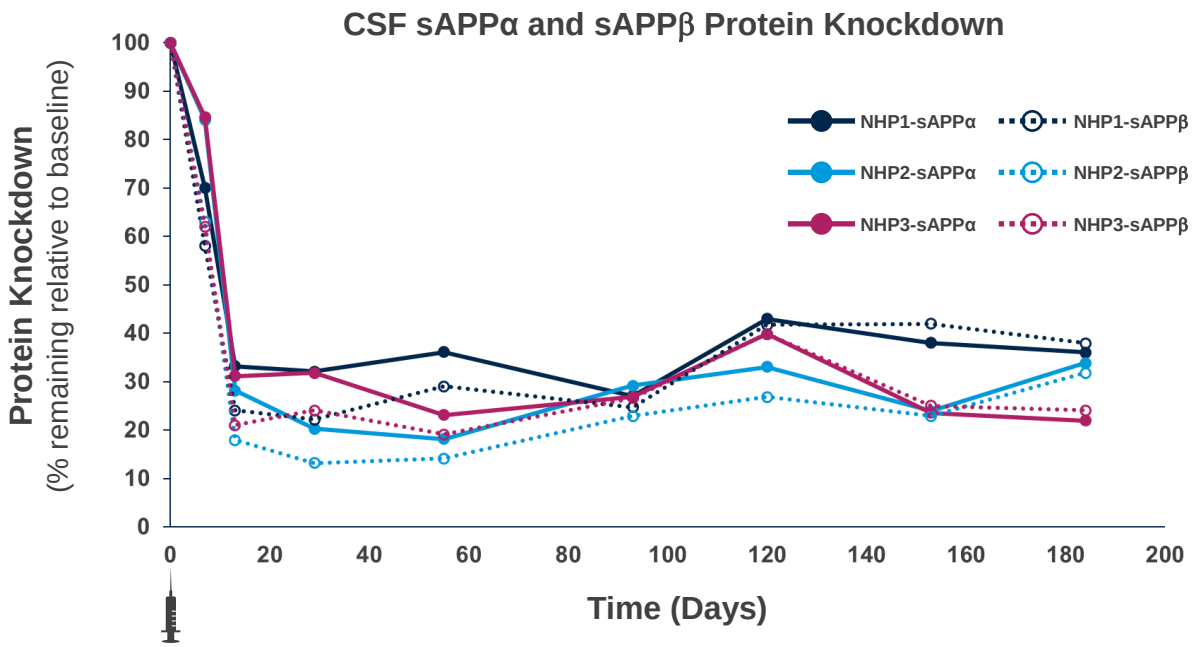
Preclinical Data Demonstrate Extensive, Potent, and Durable APP Reduction

Non-Human Primate Data of APP-targeting siRNAs

Single Intrathecal Dose of APP siRNA Distributes Throughout Spine and Brain



Single Intrathecal Dose of APP siRNA Supports Biannual or Less Frequent Regimen



Data on file

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ALN-APP Phase 1 Overview

Randomized, Double-Blind Study in Patients with Early-Onset Alzheimer's Disease (EOAD)

Part A: Single Ascending Dose
(Ongoing)

Part B: Multiple Dose
(expected to begin 2023)

- **Population**: Patients with Early Onset Alzheimer's Disease
- **Primary Objective**: Safety and tolerability of ALN-APP
- **Secondary Objective**: Pharmacology of ALN-APP
- **Exploratory Objective**: Impact of ALN-APP on disease
  - Fluid biomarkers for amyloid, tau, and neurodegeneration
  - Measures of synaptic health
  - Neuroimaging
  - Exploratory cognitive and functional clinical measures

Dose exploration continuing in Part A

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ALN-APP Phase 1 Study in EOAD

Safety Summary from Interim Analysis of Part A

Twenty patients with early-onset Alzheimer's disease enrolled in 3 single-dose cohorts in Part A of Phase 1 study

Single doses of ALN-APP well tolerated to date

- All adverse events (AEs) mild or moderate in severity
- Available CSF data, including white blood cells and protein appeared similar to placebo
- Early data for neurofilament light chain (NfL) also looked comparable to placebo

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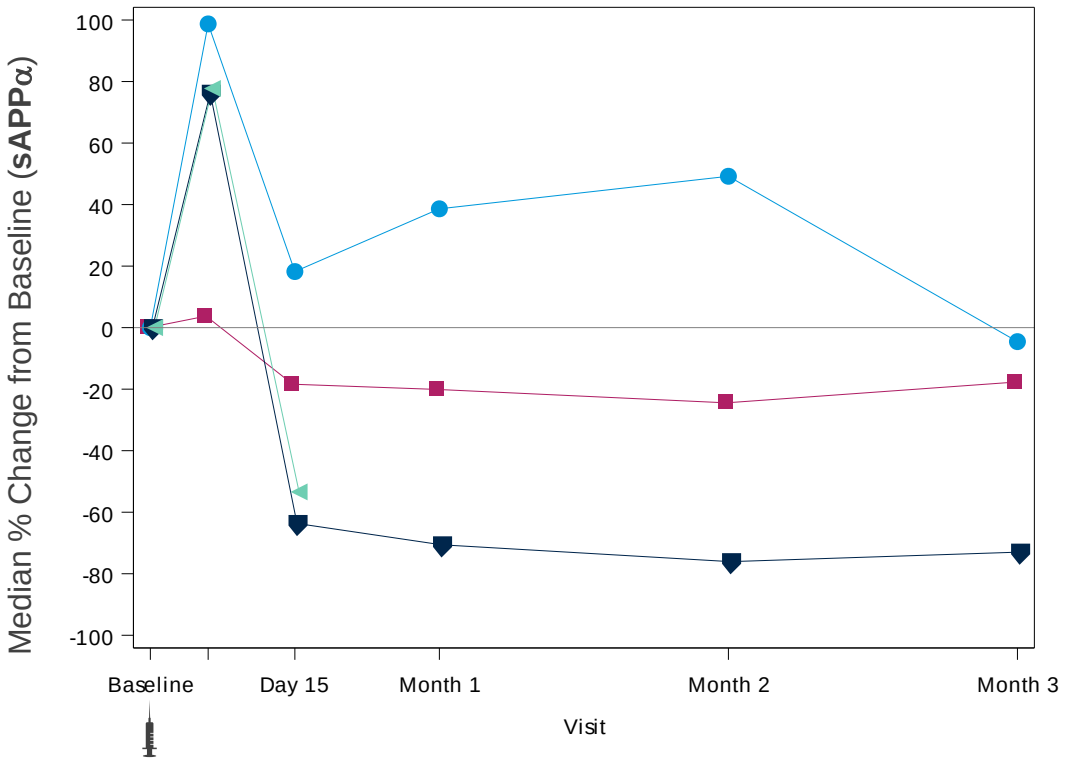
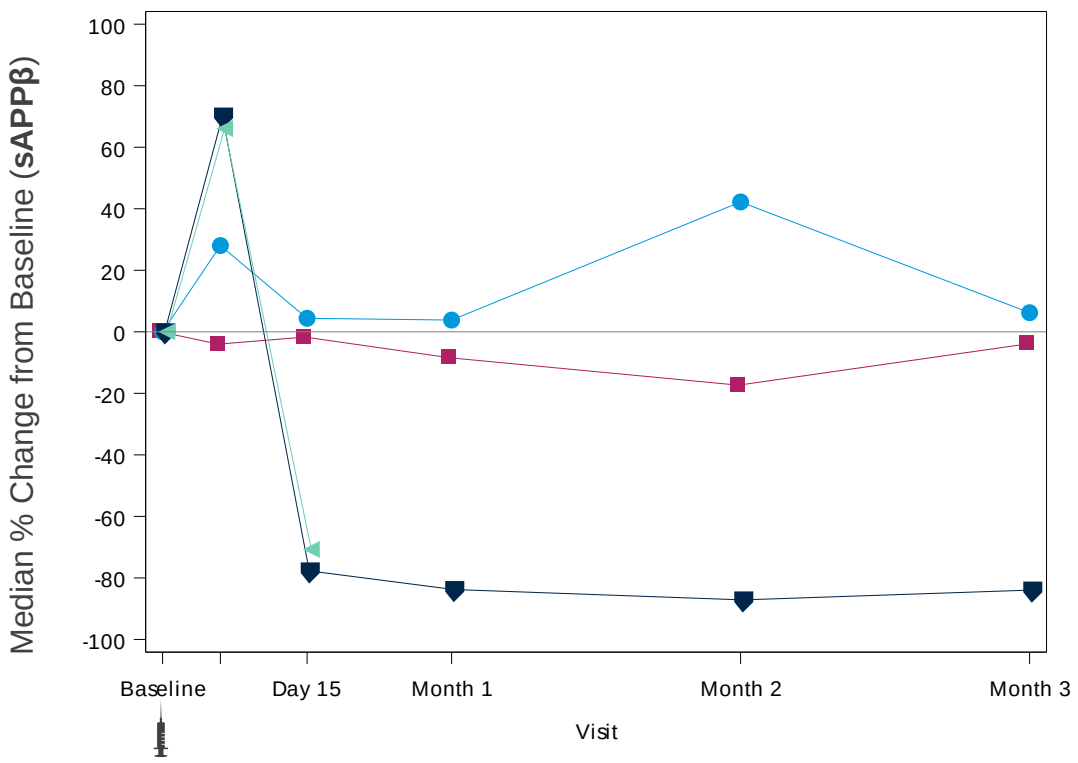
ALN-APP Phase 1 Study in EOAD – Interim Results

Robust and Sustained Reduction in sAPPα and sAPPβ in CSF at the Highest Dose Tested

Median % Change from Baseline (sAPPα)



Median % Change from Baseline (sAPPβ)



Placebo (N≥4)*
ALN-APP 50mg (N≥4)*
ALN-APP 25mg (N=4)
ALN-APP 75mg (N=4)

* Cohort (N≥4). Exact number of subjects is masked to prevent unblinding in ongoing clinical trial.

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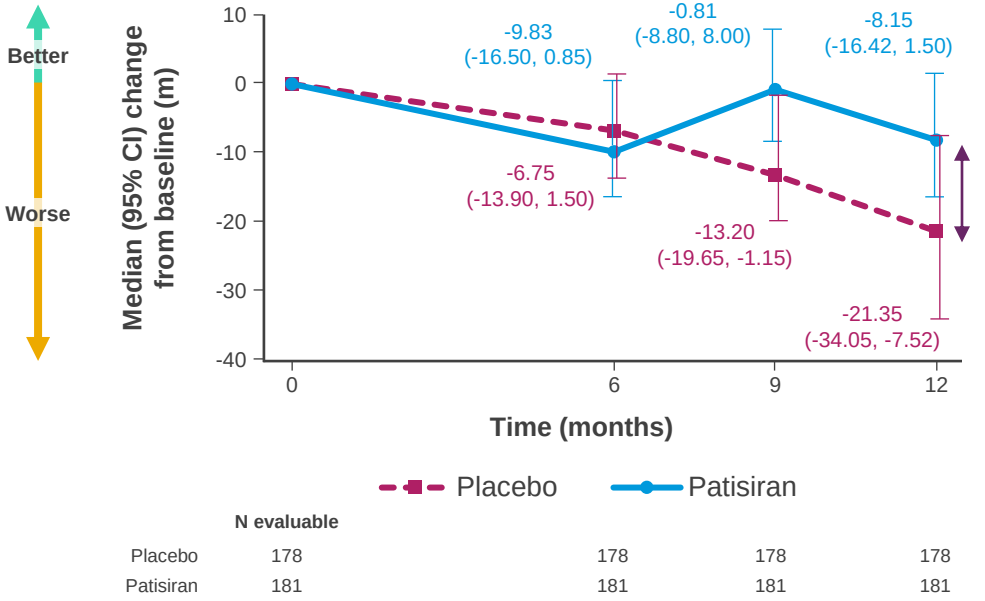
APOLLO-B Key Study Results

sNDA Accepted by FDA; Potential to Expand Label to Include ATTR Amyloidosis Patients with CM

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

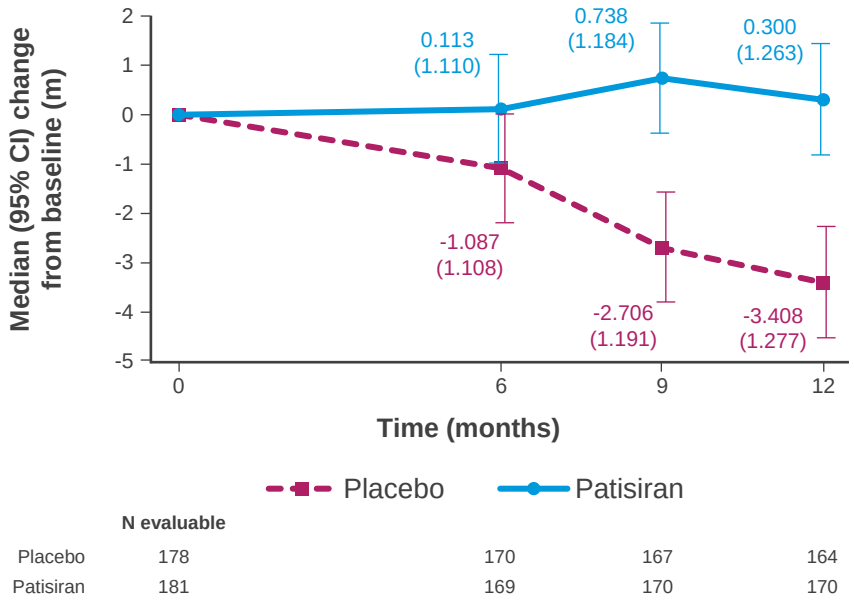
Change from Baseline in 6-MWT[a]



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.

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Vutrisiran HELIOS·B Phase 3 Study

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

N = 655
Patient Population

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

1:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Primary Endpoint

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

Select Secondary Endpoints

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

ClinicalTrials.gov Identifier: NCT04153149

HELIOS·B

Enrollment complete

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

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ALN-TTRsc04

ALN-TTRsc04

An Investigational RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis

Topline Phase 1 data expected in **late 2023**

About ALN-TTRsc04

- Potential for annual subcutaneous dosing regimen with potent and reversible effects based on preclinical data
  - Targeting >90% serum TTR reduction
- No third-party royalty obligations
- Exclusivity expected to extend beyond 2040
- Alnylam demonstrated track record for rapidly advancing innovation in ATTR amyloidosis
  - E.g., ~3 years from vutrisiran first-in-human readout to positive Phase 3 data in HELIOS-A

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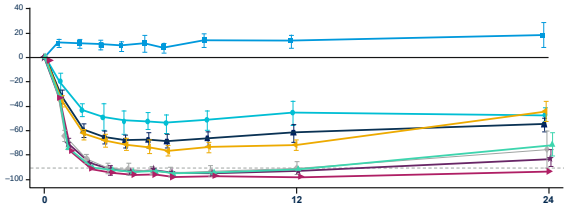
Zilebesiran: Potential Novel Treatment for Patients with Hypertension

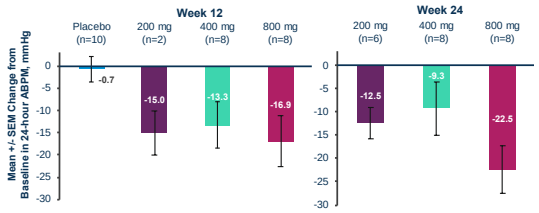
Phase 1 Data Support Development of Compelling Product Profile

Serum AGT Lowering



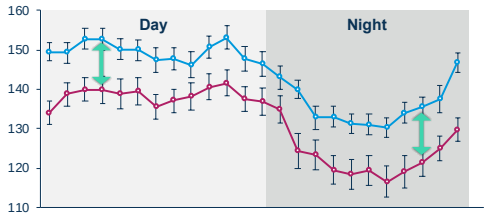
>90% mean serum AGT reduction for 6 months*

Blood Pressure Reduction



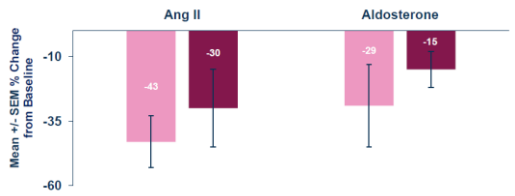
>20 mmHg SBP reduction at 6 months*

Consistent BP Reduction



Tonic BP control demonstrated over 24hr*

Change in RAAS Biomarkers



Durable reduction in Ang II & aldosterone*

KARDIA-1

Monotherapy Phase 2 Study (N = 394)

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

KARDIA-2

Combination Phase 2 Study (N ~ 630)

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

* After single dose of zilebesiran 800mg

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Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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

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

[1] Includes marketing application submissions; [2] 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; [3] Alnylam and Regeneron are evaluating potential combinations of the investigational therapeutics cemdisiran and pozelimab; [4] Novo Nordisk is leading and funding development of belcesiran; [5] Vir is leading and funding development of ALN-HBV02; [6] Regeneron is leading and funding development of ALN-HSD; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established; ** U.S. sNDA accepted; PDUFA Oct. 8, 2023. **As of May 2023**

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Jeff Poulton

Chief Financial Officer

Financial Summary and Upcoming Milestones

Q1 2023 Financial Summary

Financial Results ($ millions)	Q1 2023	Q1 2022	Q1 Reported Growth %	Q1 CER Growth %[2]
Net Product Revenues	$276	$187	48%	52%
Net Revenues from Collaborations	$36	$26	41%	
Royalty Revenues	$7	$0	-	
Total Revenues	$319	$213	50%	53%
Cost of Goods Sold and Collaborations	$55	$36	54%	
Gross Margin	$264	$178	49%	
Product Sales Gross Margin %[1]	*85%*	*87%*	-	
Non-GAAP R&D Expenses[2]	$214	$158	35%	
Non-GAAP SG&A Expenses[2]	$160	$137	17%	
Non-GAAP Operating Loss [2]	($110)	($117)		

Financial Results ($ millions)	Mar 31, 2023	Dec 31, 2022
Cash & Investments[3]	$2,071	$2,192

[1] Product Sales GM % calculation excludes $13.4M and $12.2M in Cost of Collaborations and Royalties associated with Net Revenues from Collaborations in Q1 2023 and Q1 2022, respectively.

[2] Non-GAAP R&D expenses, SG&A expenses and operating loss are non-GAAP financial measures that exclude from the corresponding GAAP measures costs related to stock-based compensation expense. CER growth rates represent growth at Constant Exchange Rates, a non-GAAP financial measure determined by comparing Q1 2023 performance (restated using Q1 2022 exchange rates) to actual Q1 2022 reported performance. A reconciliation of these non-GAAP financial measures to the comparable GAAP measures, as well as additional information regarding our use of non-GAAP financial measures, are included in the Appendix to this presentation and in our press release dated May 4, 2023, which is accessible in the Investors section of our website at www.alnylam.com.

[3] Cash, cash equivalents and marketable securities.

2023 Reiterated Full Year Guidance[1]

	Guidance	Key Assumptions
Net Product Revenue: ONPATTRO, AMVUTTRA, GIVLAARI, OXLUMO	$1,200M to $1,285M	• Assumes U.S. sNDA approval of patisiran for ATTR amyloidosis with CM by the PDUFA date on October 8th, 2023
Net Product Revenue Growth vs. 2022 at reported Fx rates	*34% to 44%*	• Uses December 31, 2022 Fx rates[1]
Net Product Revenue Growth vs. 2022 at constant exchange rates (i.e., operational growth)[2]	*34% to 44%*	• Uses 2022 actual Fx rates
Net Revenues from Collaborations & Royalties	$100M to $175M	
Non-GAAP Combined R&D and SG&A Expenses[2]	$1,575M to $1,650M	

[1] Our 2023 FY Guidance is based upon December 31, 2022 FX rates including 1 EUR = 1.07 USD and 1 USD = 131 JPY

[2] Constant exchange rate (CER) is a non-GAAP financial measure that represents growth calculated as if exchange rates had remained unchanged from those used during 2022. 2023 Non-GAAP Combined R&D and SG&A Expenses guidance is a non-GAAP financial measure that excludes from the corresponding GAAP measures stock-based compensation expense estimated at $215M - $235M. See the Financial Summary slide for more information about our use of non-GAAP financial measures.

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Alnylam 2023 Goals

			Early	Mid	Late
onpattro (patisiran) amvuttra (vutrisiran) GIVLAARI (givosiran) OXLUMO (lumasiran)		*Combined Net Product Revenue Guidance $1,200M – $1,285M*			●
PATISIRAN	ATTR Amyloidosis	FDA Approval of sNDA			●
VUTRISIRAN	ATTR Amyloidosis	Biannual Dosing Regimen Data	✓		
ALN-TTRsc04*	ATTR Amyloidosis	Phase 1 Topline Results			●
ZILEBESIRAN*	Hypertension	Complete KARDIA-2 Enrollment	●		
		KARDIA-1 Phase 2 Topline Results		●	
		KARDIA-2 Phase 2 Topline Results (at or around year-end)			●
ALN-APP*	Alzheimer's Disease	Phase 1 Topline Results	✓		
ALN-KHK*	Type 2 Diabetes	Initiate Phase 1 Study	✓		
		Phase 1 Topline Results			●
ADDITIONAL PROGRAMS		File 2-4 New INDs			●
PARTNERED PROGRAM MILESTONES					
FITUSIRAN* (Sanofi)	Hemophilia	ATLAS Phase 3 Topline Results			●
ALN-HBV02* (Vir)	Chronic HBV/HDV Infection	Phase 2 Results	●		●
ALN-PNP* (Regeneron)	NASH	Initiate Phase 1 Study	✓		

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

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Q1 2023 Financial Results

Q&A Session

Thank You!

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Q1 2023 Financial Results

Appendix

Alnylam Pharmaceuticals, Inc.

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

	Three Months Ended	
	March 31, 2023	March 31, 2022
Reconciliation of GAAP to Non-GAAP research and development:		
GAAP research and development	$ 230,569	$ 169,893
Less: Stock-based compensation expenses	(16,232)	(11,617)
Non-GAAP research and development	$ 214,337	$ 158,276
Reconciliation of GAAP to Non-GAAP selling, general and administrative:		
GAAP selling, general and administrative	$ 183,659	$ 154,471
Less: Stock-based compensation expenses	(23,715)	(17,676)
Non-GAAP selling, general and administrative	$ 159,944	$ 136,795
Reconciliation of GAAP to Non-GAAP operating loss:		
GAAP operating loss	$ (149,807)	$ (146,732)
Add: Stock-based compensation expenses	39,947	29,293
Non-GAAP operating loss	$ (109,860)	$ (117,439)

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

Alnylam Pharmaceuticals, Inc.

Reconciliation of Revenue and Growth at Constant Currency

	Three Months Ended March 31, 2023
Total TTR net product revenue growth, as reported	49 %
Add: Impact of foreign currency translation	5
Total TTR net product revenue growth at constant currency	54 %
GIVLAARI net product revenue growth, as reported	36 %
Add: Impact of foreign currency translation	3
GIVLAARI net product revenue growth at constant currency	39 %
OXLUMO net product revenue growth, as reported	66 %
Add: Impact of foreign currency translation	4
OXLUMO net product revenue growth at constant currency	70 %
Total net product revenue growth, as reported	48 %
Add: Impact of foreign currency translation	4
Total net product revenue growth at constant currency	52 %
Total revenue growth, as reported	50 %
Add: Impact of foreign currency translation	3
Total revenue growth at constant currency	53 %

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