Glaucienne
Living with AHP (Brazil)

First Quarter 2021 Financial Results

April 29, 2021

Alnylam® PHARMACEUTICALS

Agenda

Welcome

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

Overview

- John Maraganore, Ph.D.
  Chief Executive Officer

Commercial Highlights

- Tolga Tanguler
  Chief Commercial Officer

Alnylam Clinical Pipeline

- Akshay Vaishnaw, M.D., Ph.D.
  President of R&D

Financial Summary and Guidance

- Jeff Poulton
  Chief Financial Officer

2021 Goals Update

- Yvonne Greenstreet, MBChB, MBA
  President and Chief Operating 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 ability to achieve our "Alnylam P^{5}x25" strategy, the potential expansion of the ATTR amyloidosis franchise, plans for additional global regulatory filings and the continuing product launches of our approved products, the achievement of additional pipeline and regulatory milestones, including for vutrisiran, patisiran and lumasiran, expectations regarding FDA review of inclisiran, conditions at the third party manufacturer where inclisiran is manufactured and the expected timing of resubmission of the inclisiran NDA by Novartis, the potential market opportunity for Leqvio and fitusiran, the potential opportunity for RNAi therapeutics in prevalent diseases, expectations relating to continued revenue growth for our approved products and the expected range of net product revenues and net revenues from collaborations and royalties for 2021, and the expected range of aggregate annual GAAP and non-GAAP R&D and SG&A expenses for 2021. 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; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO 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 the 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 Annual Report on Form 10-K 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 and unrealized gains on marketable equity securities. 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 unrealized gains 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 are reported as their sole purpose is to adjust amounts on the balance sheet.

John Maraganore, Ph.D.

Chief Executive Officer

Overview

TRANSFORMATIONAL MEDICINES

ROBUST & HIGH-YIELD R&D PIPELINE

ORGANIC PRODUCT ENGINE

Our New 5-Year Strategy

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

Corporate Responsibility at Alnylam

Tolga Tanguler

Chief Commercial Officer

Commercial Highlights

ONPATTRO® Launch Update: Q1 2021

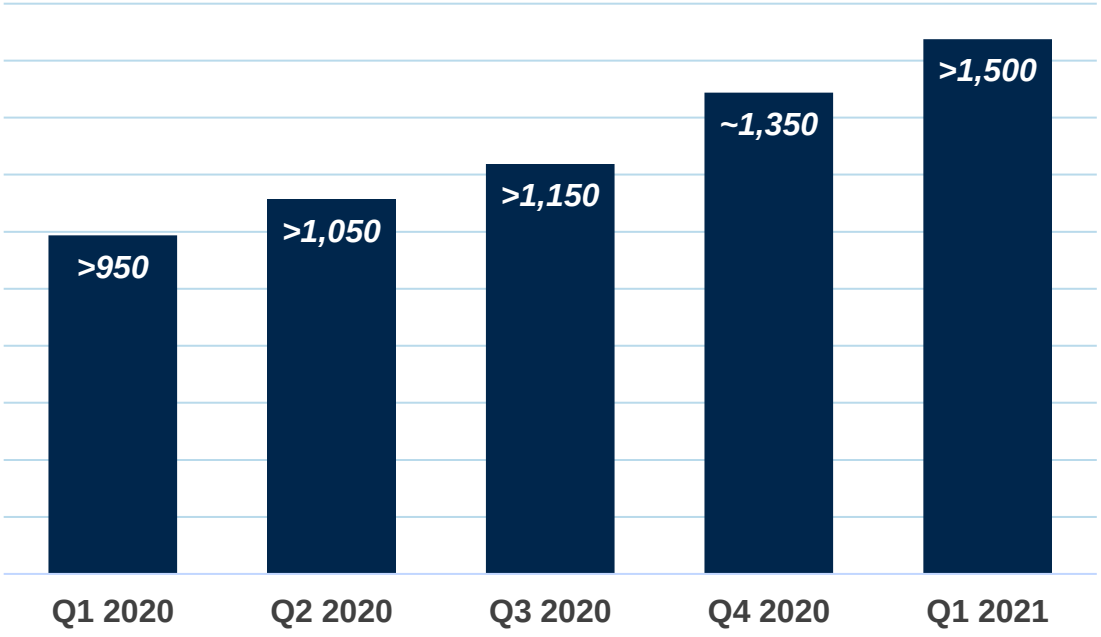
Steady and Continued Growth

$102M

ONPATTRO Global Q1 2021 Net Product Revenues

>1,500

Patients Worldwide on Commercial ONPATTRO at end of Q1 2021



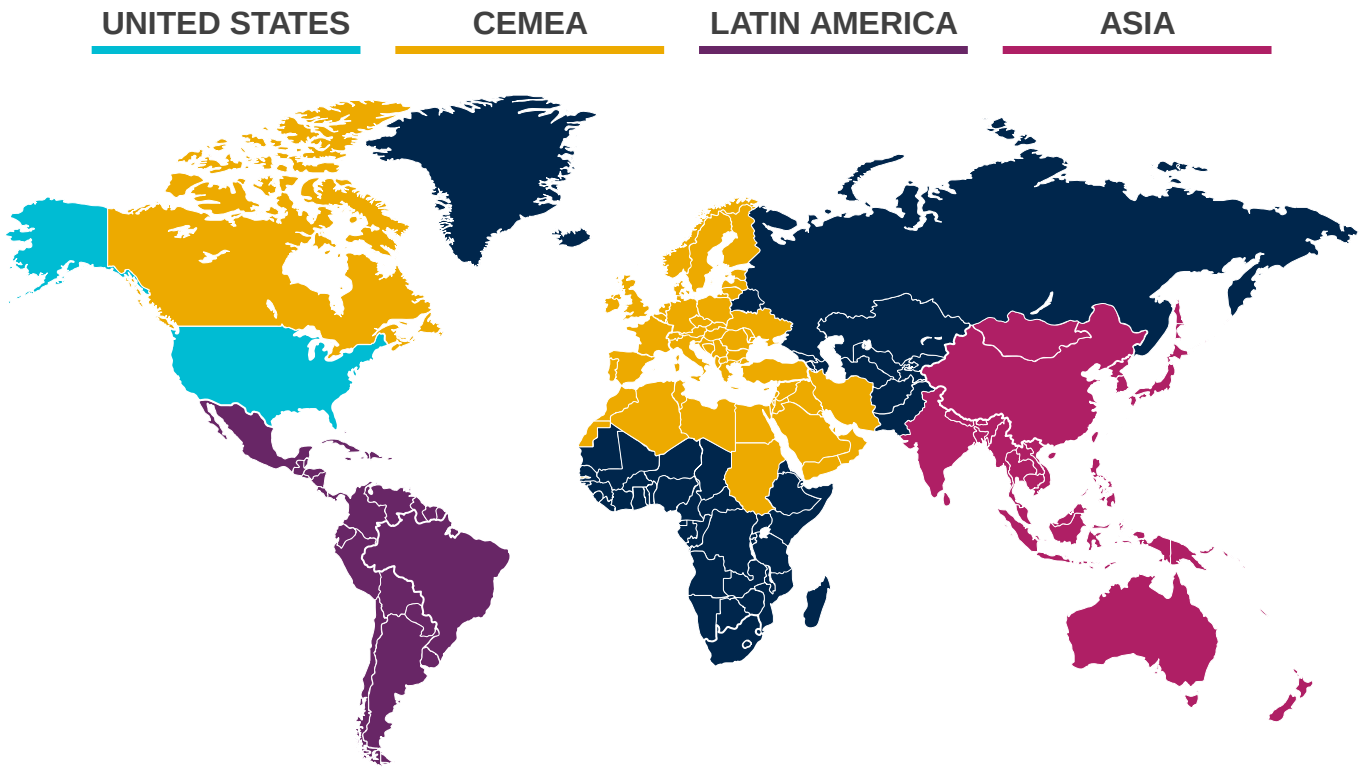
Q1 U.S. Highlights

- Steady, continuous patient growth; notable growth in new prescribers
- Continued trend of ONPATTRO used to treat the polyneuropathy of hATTR amyloidosis in mixed phenotype hATTR amyloidosis patients who are on a stabilizer for cardiomyopathy

ONPATTRO Global Commercialization

Increasing Access and Value Recognition

- Progress with global ONPATTRO availability
  - Achieved regulatory approval in Taiwan
  - Over 30 countries now selling ONPATTRO through direct reimbursement, named patient sales, or reimbursed expanded access
  - Uptake observed from both first-line treatment in hATTR patients with PN and switching from other products, including stabilizers



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

CEMEA: Canada, Europe, Middle East, North Africa

GIVLAARI® Launch Update: Q1 2021

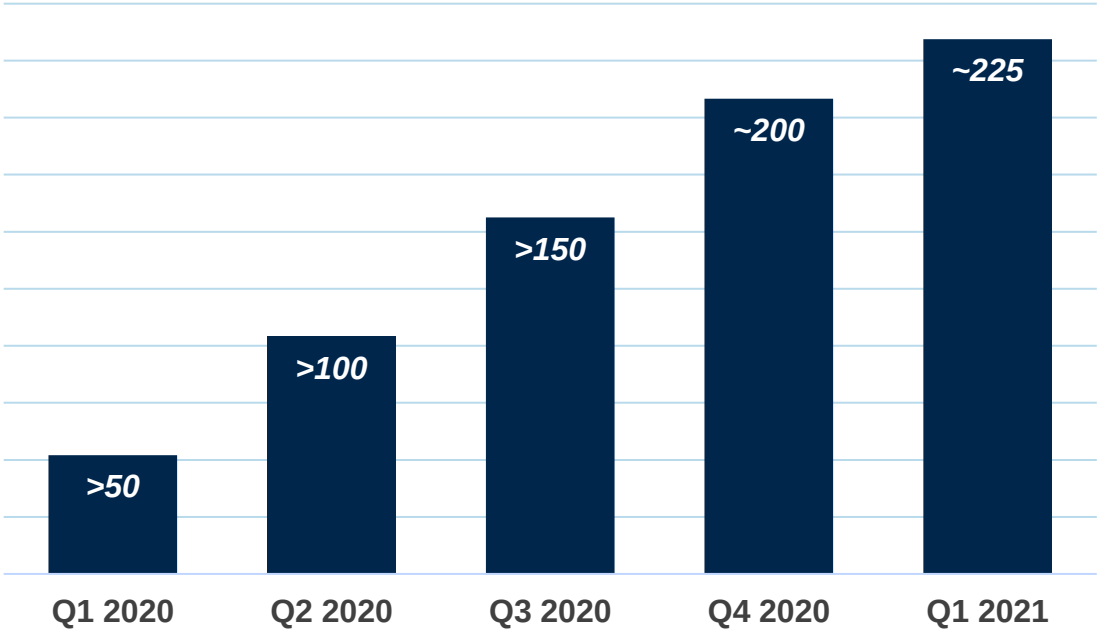
Continued Progress with Uptake and Access

$25M

GIVLAARI Global Q1 2021 Net Product Revenues

~225

Patients Worldwide on Commercial GIVLAARI at end of Q1 2021



Q1 U.S. Highlights

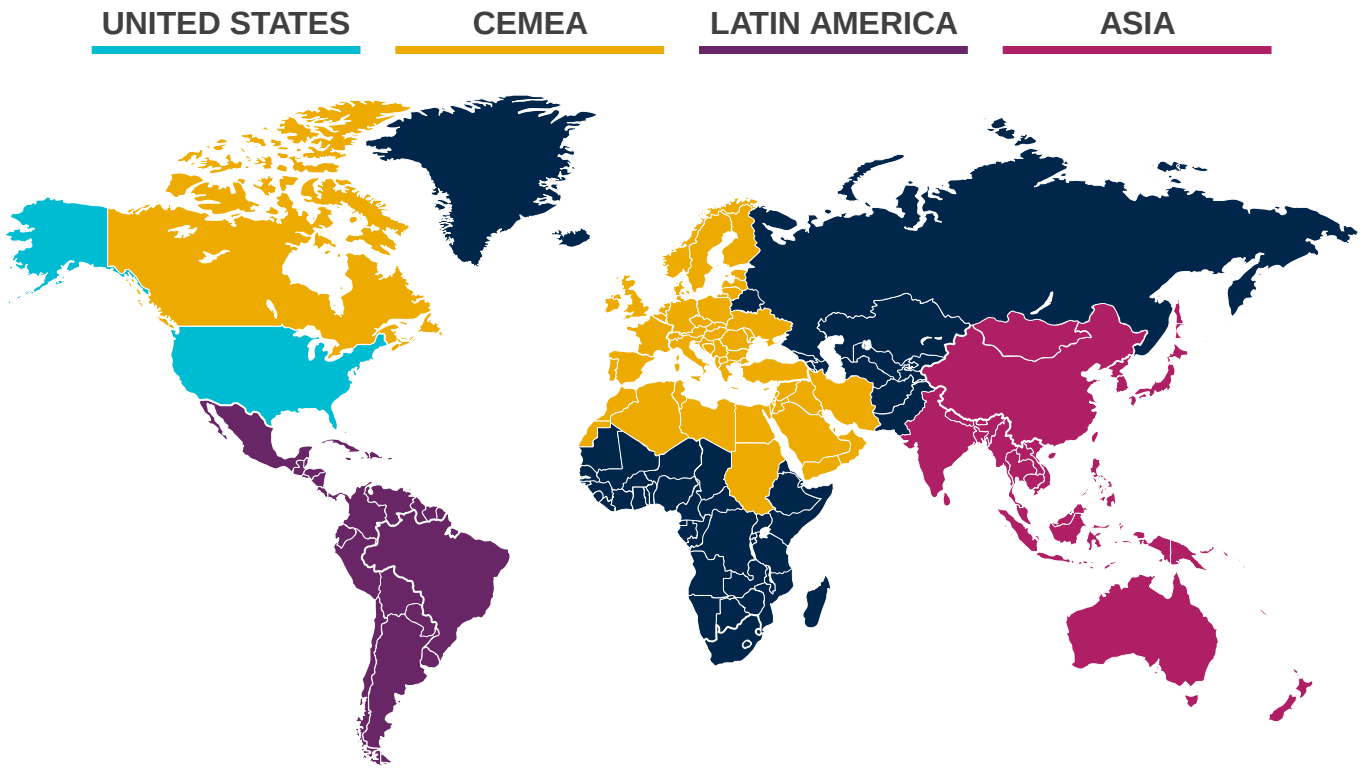
>10 Value-Based Agreements (VBAs) finalized

>98% U.S. lives with confirmed access to GIVLAARI, if prescribed

GIVLAARI Global Commercialization

Ensuring GIVLAARI Availability Around the World

- Progress with global GIVLAARI availability
  - Recent launch in Italy
  - Achieved approval in Switzerland
  - Japan JNDA review on track for approval mid-year



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

CEMEA: Canada, Europe, Middle East, North Africa

OXLUMO® Launch Update: Q1 2021

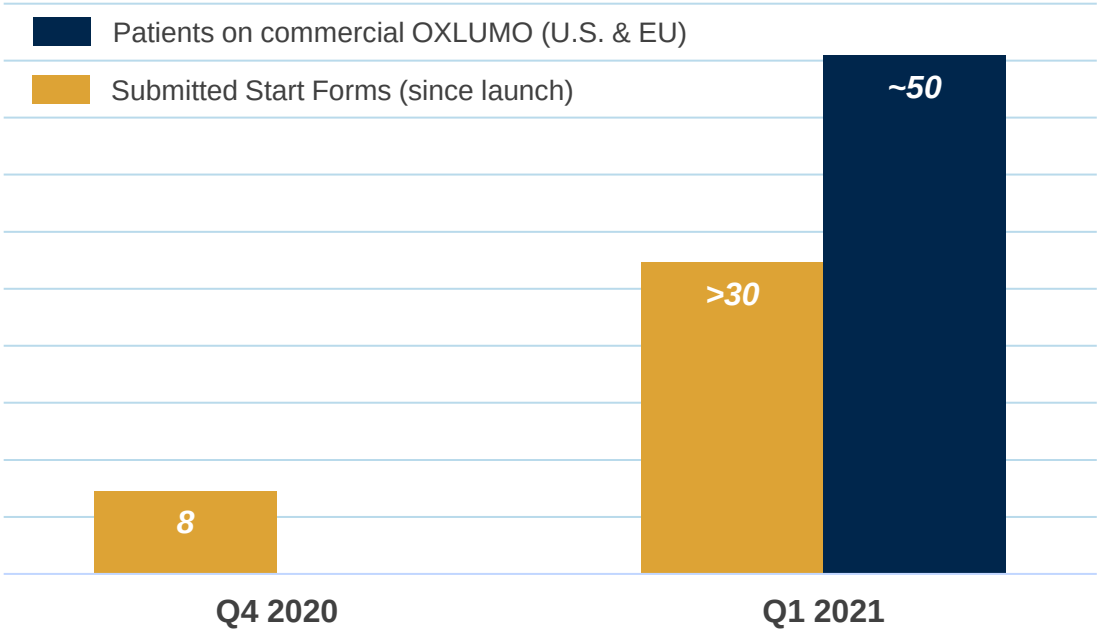
Strong First Quarter Performance

$9M

OXLUMO Global Q1 2021 Net Product Revenues

~50

Patients Worldwide on Commercial OXLUMO at end of Q1 2021



Q1 U.S. Highlights

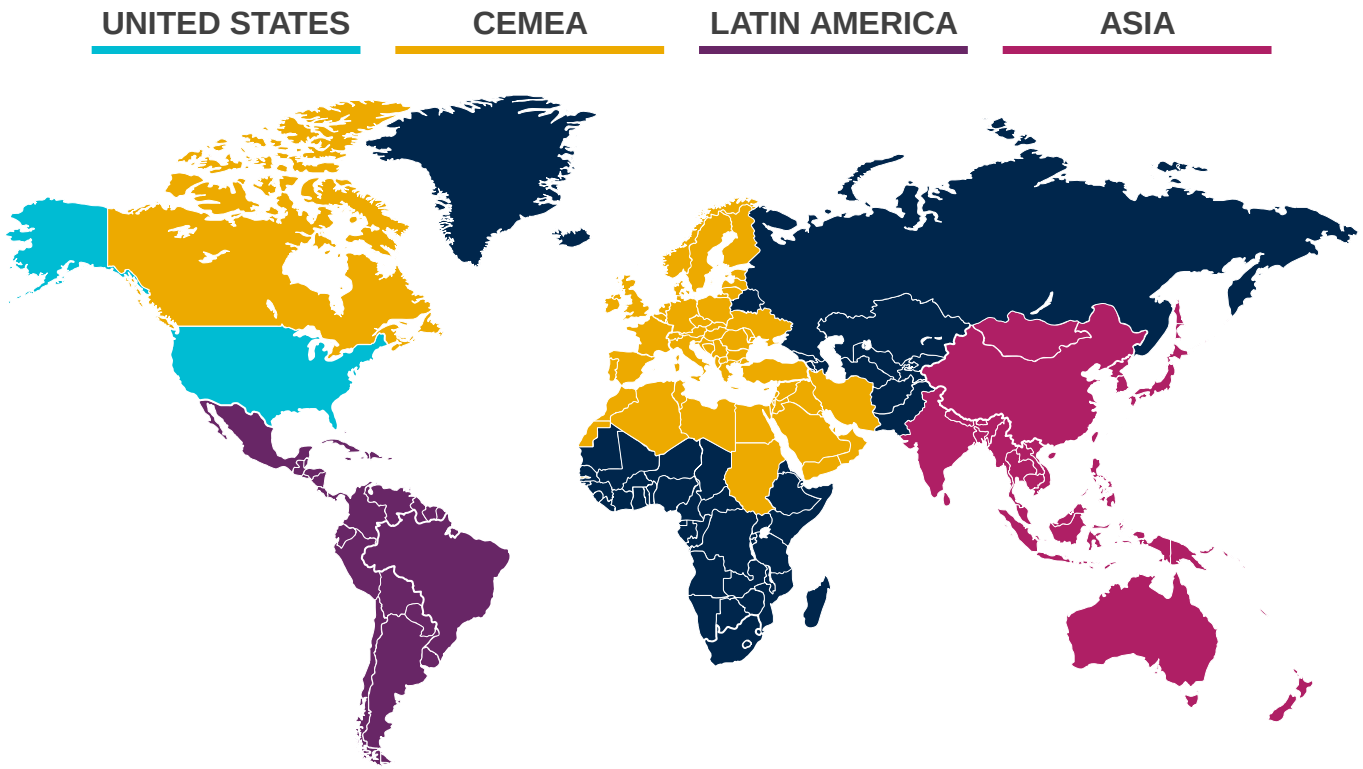
- **>5** Value-Based Agreements (VBAs) finalized
- **~2/3** covered U.S. lives with confirmed access to OXLUMO, if prescribed

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

OXLUMO Global Commercialization

Ensuring OXLUMO Availability Around the World

- Progress with global OXLUMO availability
  - Recent launch in Germany
  - ATU supply in France
  - Named patient sales in other countries
  - Broad utilization across age groups and EGFR categories



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

CEMEA: Canada, Europe, Middle East, North Africa

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

President of R&D

Alnylam Clinical Pipeline

Patisiran APOLLO-B Phase 3 Study

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

N ~ 300
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
  - TTR stabilizer naïve and/or TTR stabilizer progressor
- 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

Key Secondary Endpoints

- Cardiomyopathy symptoms and health status
- Death and hospitalization outcomes
- Cardiac biomarkers

12-Month Treatment Extension

APOLLO-B

Enrollment completion expected **early 2021**

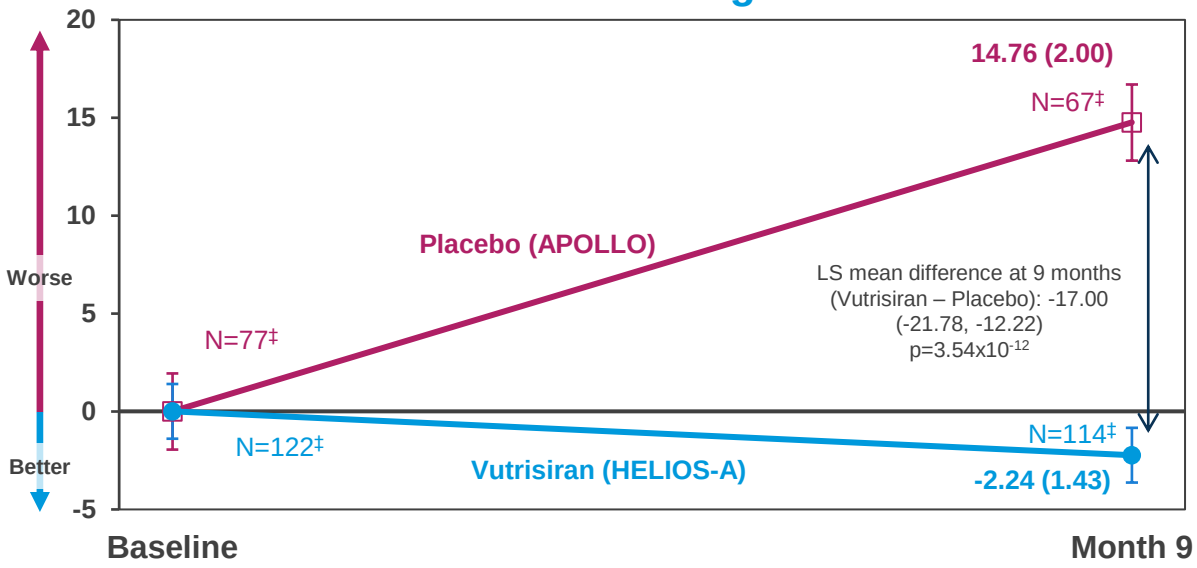
Topline results expected **mid-2022**

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

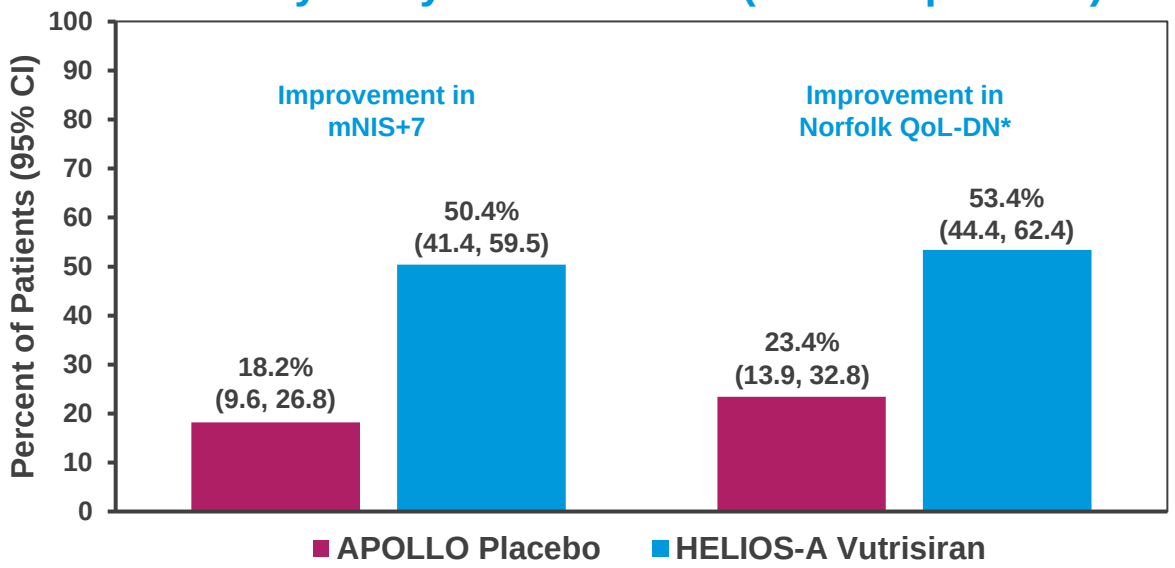
HELIOS-A 9-Month Results

Randomized, Open-Label Study in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy (N=164)

mNIS+7 LS Mean Change from Baseline



Binary Analysis at Month 9 (mITT Population)



Both secondary endpoints met

- Improvement demonstrated in quality of life and 10-meter walk test

Positive exploratory cardiac endpoint result

- Improvement in NT-proBNP biomarker in cardiac subpopulation, relative to placebo (p=0.0016); additional exploratory cardiac data at Month 18 planned to be presented in Late 2021

Encouraging safety and tolerability profile

- No drug-related discontinuations or deaths; two SAEs deemed drug-related: dyslipidemia, urinary tract infection
- Treatment emergent AEs in ≥10% of vutrisiran patients all common in disease natural history and occurred at similar or lower rates than placebo comparator group
  - Include diarrhea, pain in extremity, fall and urinary tract infections
- Low incidence of injection site reactions (ISRs), all mild and transient
- No safety signals regarding liver function tests, hematology or renal function related to vutrisiran

Adams et al., *AAN*, April 2021 as to primary endpoint and safety/tolerability at Month 9; additional data presented by Alnylam in conference call held April 19, 2021

APOLLO refers to the randomized, placebo-controlled Phase 3 study of ONPATTRO (patisiran) in hATTR patients with polyneuropathy (Adams et al, NEJM, 2018). HELIOS-A compares vutrisiran treated hATTR patients with polyneuropathy to the prespecified external placebo group from APOLLO

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

ClinicalTrials.gov Identifier: NCT04153149

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

HELIOS·B

Enrollment completion expected **late 2021**

Study includes optional interim analysis

ILLUMINATE Phase 3 Program

Robust Registrational Program to Evaluate Lumasiran Across all Ages and Full PH1 Disease Spectrum

ILLUMINATE

ILLUMINATE•A

Double-blind, placebo-controlled trial in PH1 patients at least 6 years old with preserved renal function

Full results presented
June 2020

ILLUMINATE•B

Single arm, open-label study in PH1 patients less than 6 years old with preserved renal function

Full results presented
October 2020

ILLUMINATE•C

Single arm, open-label study in PH1 patients with impaired renal function, including advanced disease

Enrollment completed;
Topline results expected
in **mid-2021**

Phase 2 study in recurrent renal stones expected to initiate in 2021

Driving Innovation Through Late-Stage Partnered Programs

Leqvio® (inclisiran)

NOVARTIS

Blackstone

Hypercholesterolemia

40%	Adults WW with high LDL-C; ASCVD leading cause of death WW
>50M	Patients in key markets with ASCVD or FH on current SOC not at goal
7%	Treated patients statin intolerant
>60%	Patients treated with statins +/- ezetimibe do not meet goal[1]

Approved in EU

CRL in U.S. related to inspection; no efficacy, safety concerns raised; Novartis response to be submitted Q2-Q3 2021

Fitusiran

SANOFI

Hemophilia A or B, with and without inhibitors

~200K	Patients WW with hemophilia A or B, with and without inhibitors
~75%	Patients switched to emicizumab due to convenience (less frequent dosing, SC)[2]
<10%	Emicizumab patients on monthly dosing[3]
~90%	Emicizumab patients experienced acute bleeds[2]

Dosing resumed in ATLAS studies[4]

Initial data expected late 2021/early 2022

NDA submission expected H2 2022 based on revised dosing regimen[5]

[1] Boekholdt et al. Very Low LDL-C levels and CVD Risk JACC VOL 64.No5 2014:485-94; [2] Consumer Awareness, Trial, and Usage study among patients conducted over 359 Adult patients and caregivers surveyed online in April 2019, of which 131 were Adult Hemophilia A patients and 78 were Hemophilia A caregivers. Patients who switched to emicizumab answered questions specific to their treatment experience'; [3] 2019 Specialty Pharmacy data obtained through Specialty Pharmacy Distributors, Hemophilia Alliance HTCs and Direct HTCs; [4] Previous reports of thromboembolic events were associated with high levels of antithrombin reduction to < 10% of normal; [5] Sanofi to evaluate once-every-2 monthly 50 mg dosing regimen for fitusiran that can be titrated up in frequency to once-monthly and in dose to 80 mg depending on antithrombin levels achieved.

RNAi Therapeutics Profile Supports Potential Expansion to Prevalent Diseases

- Durability
- Clamped pharmacology
- Established safety profile
- Improved access

RARE

ONPATTRO: hATTR-PN[1]
GIVLAARI
OXLUMO
Vutrisiran: hATTR-PN[3]
Fitusiran
DCR-A1AT
ALN-APP
ALN-HTT

SPECIALTY

Patisiran: ATTR-CM[2]
Vutrisiran: ATTR-CM[3]
Cemdisiran

PREVALENT

Leqvio® (inclisiran)[4]
ALN-HBV02 (VIR-2218)
ALN-AGT
ALN-HSD
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 submitted seeking approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis 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 EU for the treatment of adults with hypocholesterolemia or mixed dyslipidemia; in the U.S., Novartis received a Complete Response Letter on the NDA for inclisiran and plans to resubmit an NDA in Q2/Q3 2021.

Over 25 Preclinical Programs in Four Tissues Feeding Sustainable Innovation

Alnylam
- ALN-XDH
- ALN-KHK
- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

Alnylam/Regeneron
- ALN-PNP
- ALN-REGN-L2
- ALN-REGN-L4
- ALN-REGN-L5

Alnylam/Regeneron
- ALN-APP
- ALN-HTT
- ALN-REGN-C3
- ALN-REGN-C4
- ALN-REGN-C5
- ALN-REGN-C6
- ALN-REGN-C7
- ALN-REGN-C8
- ALN-REGN-C9

Alnylam
- ALN-TTRoc

Alnylam/Regeneron
- ALN-REGN-E1
- ALN-REGN-E2
- ALN-REGN-E3
- ALN-REGN-E4

Alnylam/Vir
- ALN-COV
- ALN-VIR2 (ACE2)
- ALN-VIR3 (TMPRSS2)

2-4 *INDs per year from organic product engine (4+ planned by end-'25)*

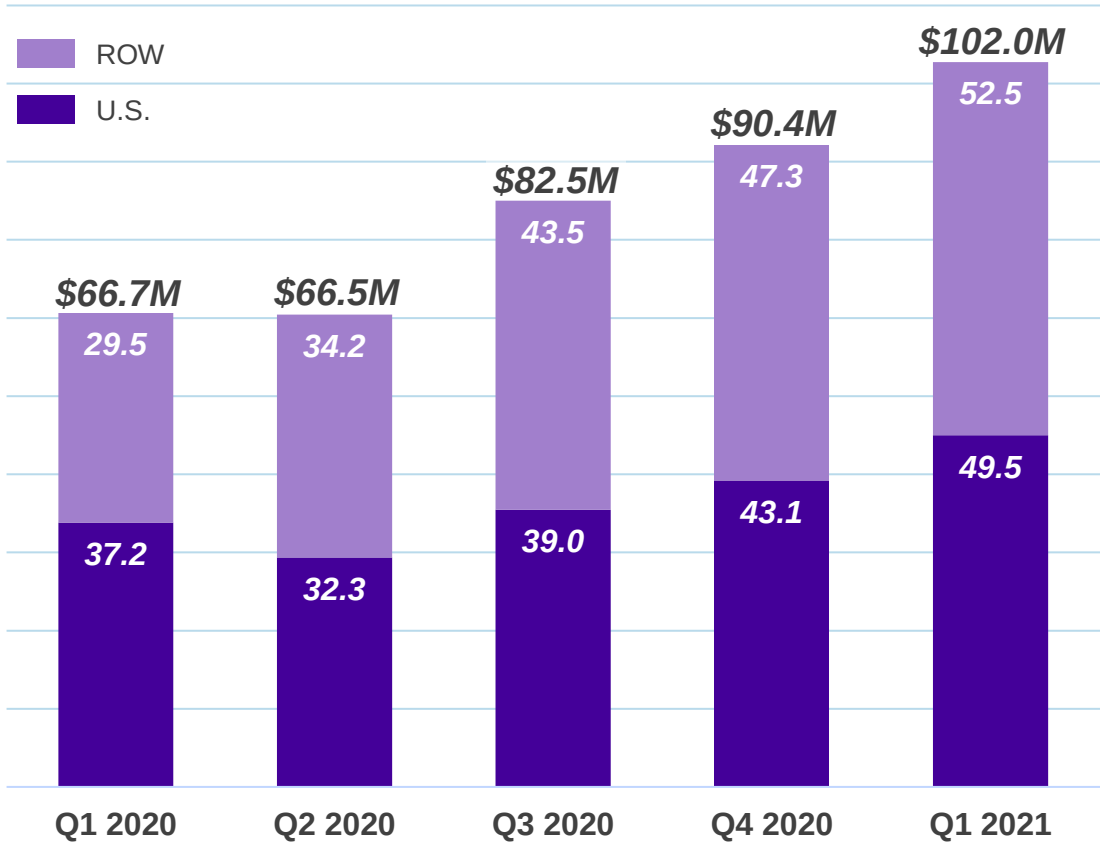
Jeff Poulton

Chief Financial Officer

Financial Summary and Guidance

Global ONPATTRO Q1 2021 Performance

Revenue ($M)



Q1 Highlights

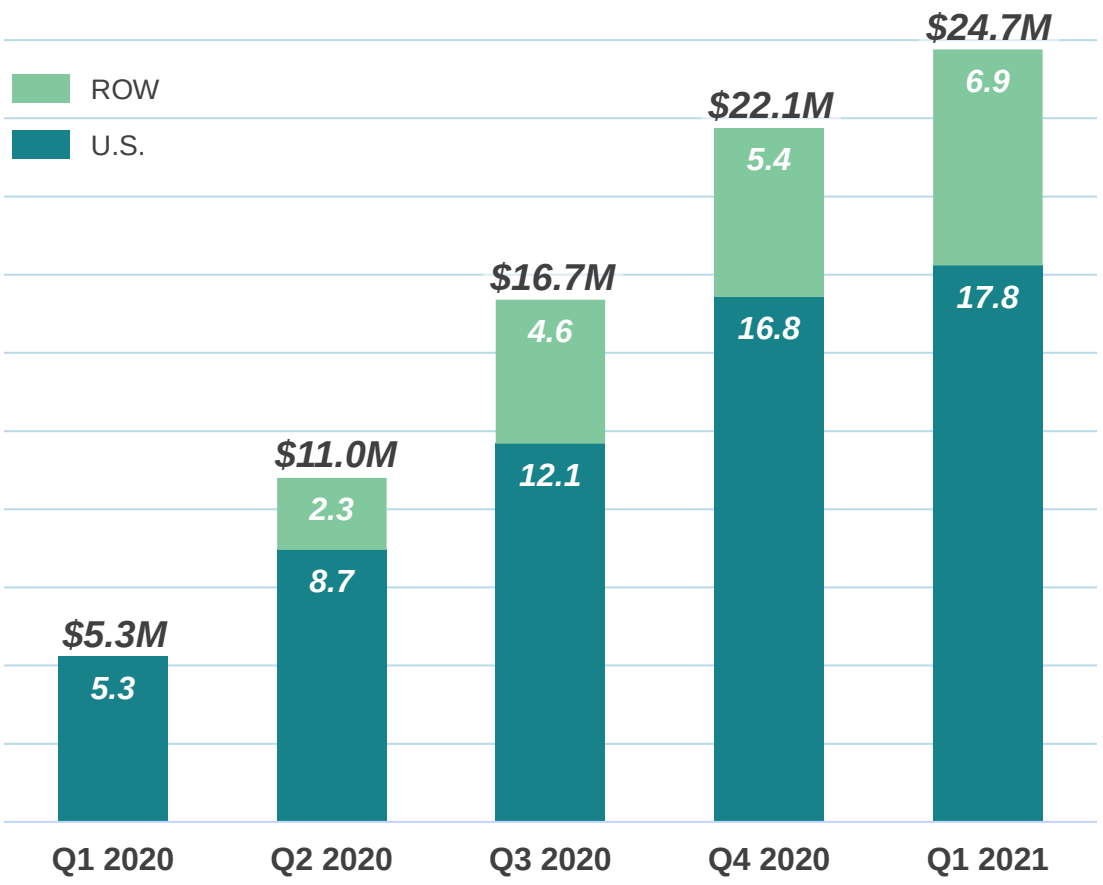
	YoY % Growth	QoQ % Growth
U.S.	33%	15%
ROW	78%	11%
Global	53%	13%

- Steady and continuous patient growth continues across key markets (>1,500 commercial patients at end of Q1)
- 3rd consecutive quarter of double-digit quarter on quarter global growth
- U.S. Q1 demand growth ~+4%, with additional growth favorably impacted by increase in inventory in distribution channel and decrease in gross to net sales deductions

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

Global GIVLAARI Q1 2021 Performance

Revenue ($M)



Q1 Highlights

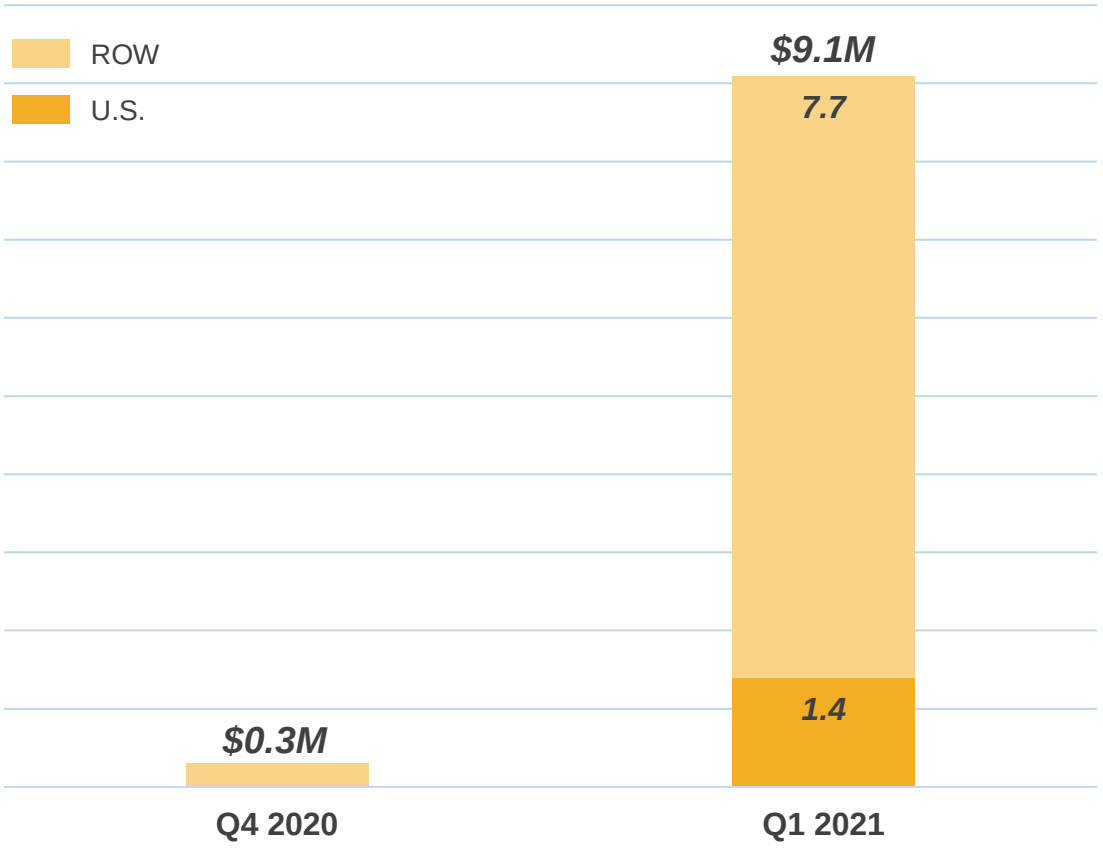
	YoY % Growth	QoQ % Growth
U.S.	237%	6%
ROW	N/A	28%
Global	368%	11%

- ~ 225 global patients on therapy since launch
- U.S. growth unfavorably impacted by increase in gross to net deductions in Q1
- Continued progress with VBAs in U.S. with >10 finalized and confirmed access for over 98% of covered lives
- Continued progress with market access efforts across Europe, with recent launch in Italy

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

Global OXLUMO Q1 2021 Performance

Revenue ($M)



Q1 Highlights

- Received >30 Start Forms in U.S. and attained ~50 patients on commercial treatment in U.S. and Europe since launch
- Strong initial quarter of sales in Europe primarily driven by launch in Germany and ATU sales in France
- Encouraging initial uptake in both pediatric and adult patient populations
- Continued strong progress toward establishing value-based agreements (VBAs), with >5 VBAs finalized to date with commercial payers and confirmed access for ~2/3 of covered U.S. lives

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

Q1 2021 Financial Summary

Financial Results ($ millions)	Q1 2021	Q1 2020	YoY % Change
ONPATTRO Net Product Revenues	$102.0	$66.7	53%
GIVLAARI Net Product Revenues	$24.7	$5.3	368%
OXLUMO Net Product Revenues	$9.1	-	N/A
Total Net Product Revenues	$135.8	$71.9	89%
Net Revenues from Collaborations	$41.8	$27.5	52%
Total Revenues	$177.6	$99.5	79%
Cost of Goods Sold and Collaborations	$31.1	$13.3	134%
GM as % of Total Revenues[1]	*82.5%*	*86.6%*	-
Non-GAAP R&D Expenses[2]	$161.5	$153.5	5%
Non-GAAP SG&A Expenses[2]	$115.5	$108.2	7%
Non-GAAP Operating Loss[2]	($130.6)	($175.6)	(26%)

Financial Results ($ millions)	Mar 31, 2021	Dec 31, 2020
Cash & Investments[3]	$1,709.5	$1,874.4

[1] GM as a % of Total Net Product Revenues for Q1 2021 is 83.0% and Q1 2020 is 81.5% (Q1 2021 excludes $8.0M Cost of Collaborations associated with Net Revenues from Collaborations).
[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] Cash, cash equivalents and marketable securities
See Appendix for a reconciliation between GAAP and non-GAAP measures

2021 Full Year Guidance Reiterated

	FY 2021 Guidance	Projected 2021 Growth (using mid-point of guidance)
Net Product Revenues (ONPATTRO, GIVLAARI, OXLUMO)	$610M – $660M	+76%
Net Revenues from Collaborations & Royalties	$150M – $200M	+33%
Non-GAAP Combined R&D and SG&A Expenses[1]	$1,175M – $1,275M	+15%

[1] 2021 Non-GAAP Combined R&D and SG&A Expenses guidance excludes stock-based compensation expense estimated at $160M - $180M

Yvonne Greenstreet, MBChB, MBA

President and Chief Operating Officer

2021 Goals Update

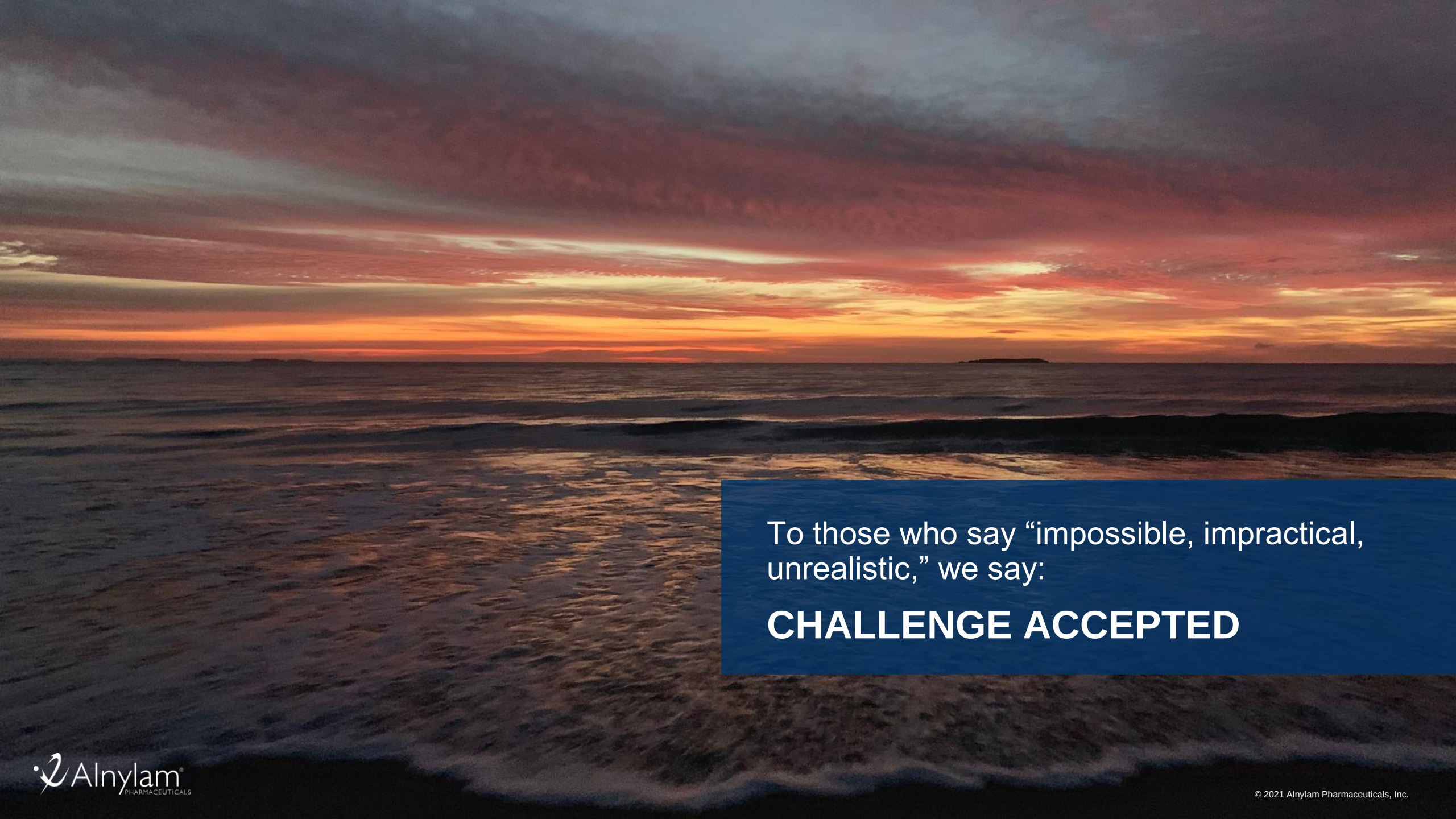
Alnylam 2021 Goals

		Early	Mid	Late
onpattro® (patisiran) lipid complex injection 10 mg/5 mL (hATTR/ATTR Amyloidosis)	Global Commercial Execution	●	●	●
	Complete APOLLO-B Phase 3 Enrollment	●		
GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL (Acute Hepatic Porphyria)	Global Commercial Execution	●	●	●
	Japan Approval		●	
OXLUMO™ (lumasiran) for injection 94.5 mg/0.5 mL (Primary Hyperoxaluria Type 1)	Global Commercial Execution	●	●	●
	Brazil Approval	●		
	ILLUMINATE-C Phase 3 Topline		●	
VUTRISIRAN (hATTR/ATTR Amyloidosis)	HELIOS-A Phase 3 Topline – 9 Month Endpoints	✓		
	File NDA for hATTR-PN	✓		
	Initiate q6M Dose Regimen Study	●		
	HELIOS-A Phase 3 Topline – 18 Month Endpoints (incl. exploratory cardiac)			●
	HELIOS-B Phase 3 Enrollment			●
ALN-AGT (Uncontrolled Hypertension)	Initiate KARDIA Phase 2 Program		●	
ADDITIONAL CLINICAL PROGRAMS	Continue to advance early/mid-stage pipeline; File 2-4 new INDs; Present clinical data	●	●	●
PARTNERED PROGRAMS				
Leqvio® (inclisiran) (Hypercholesterolemia)	FDA Approval (guidance pending)			
	Support, as Needed, Novartis on Global Commercial Execution	●	●	●
	Support, as Needed, Novartis on ORION-4 CVOT Phase 3 Enrollment	●	●	●
FITUSIRAN (Hemophilia)	Support, as Needed, Sanofi on ATLAS Phase 3 Studies	●	●	●

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

Q1 2021 Financial Results

Q&A Session



Alnylam PHARMACEUTICALS

Q1 2021 Financial Results

Appendix

Alnylam Pharmaceuticals, Inc.

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

	Three Months Ended	
	March 31, 2021	March 31, 2020
Reconciliation of GAAP to Non-GAAP research and development:		
GAAP Research and development	$ 185,899	$ 169,571
Less: Stock-based compensation expenses	(24,375)	(16,049)
Non-GAAP Research and development	$ 161,524	$ 153,522
Reconciliation of GAAP to Non-GAAP selling, general and administrative:		
GAAP Selling, general and administrative	$ 146,859	$ 126,761
Less: Stock-based compensation expenses	(31,315)	(18,529)
Non-GAAP Selling, general and administrative	$ 115,544	$ 108,232
Reconciliation of GAAP to Non-GAAP operating loss:		
GAAP operating loss	$ (186,254)	$ (210,158)
Add: Stock-based compensation expenses	55,690	34,578
Non-GAAP operating loss	$ (130,564)	$ (175,580)

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