First Quarter 2019 Financial Results

May 1, 2019

Alnylam® PHARMACEUTICALS

Agenda

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

Q1 2019 Overview
- John Maraganore, Ph.D.
  Chief Executive Officer

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

Commercial/Med Affairs Highlights
- Barry Greene
  President

Financial Summary and Guidance
- Manmeet Soni
  Chief Financial Officer

2019 Goals Update
- Yvonne Greenstreet, MBChB, MBA
  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. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally; our ability to successfully expand the indication for ONPATTRO® (patisiran) in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent annual report on Form 10-K under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance 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 contains non-GAAP financial measures, including expenses adjusted to exclude certain non-cash expenses and non-recurring gains outside the ordinary course of the Company’s business. These measures are not in accordance with, or an alternative to, GAAP, and may be difference 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 presented herein are stock-based compensation expense and the gain on litigation settlement. The Company has 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 the Company’s stock price, which impacts the fair value of these awards. The Company has excluded the impact of the gain on litigation settlement because the Company believes this item is a one-time event occurring outside the ordinary course of the Company’s business.

John Maraganore, Ph.D.
Chief Executive Officer

Q1 2019 Overview

Alnylam Snapshot

Sustainable Value Creation Potential

Strong Launch Progress

Productive R&D Engine

Positioned for Future Growth

Strong Balance Sheet


Alnylam®
PHARMACEUTICALS
2020
3 STArs
3 Marketed Products
10 Clinical Programs
4 Late Stage Programs

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-MWD at 12 months

Key Secondary Endpoints

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

12-Month Treatment Extension

APOLLO-B

Expected to initiate in **mid-2019**

* Subject to protocol finalization; 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-MWD: 6-Minute Walk Distance

Vutrisiran HELIOS·A Phase 3 Study

Randomized, Open-Label Study in Hereditary ATTR Amyloidosis Patients

N ~ 160
Patient Population

- hATTR amyloidosis; any TTR mutation
- Neuropathy Impairment Score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

3:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Reference Comparator
(patisiran)

9-Month Efficacy^

- Assessment vs. APOLLO placebo arm

18-Month Efficacy

- Assessment vs. APOLLO placebo arm

Open-Label Extension

HELIOS·A

Efficacy Assessments vs. APOLLO placebo arm

Co-Primary Endpoints

- Change in mNIS+7 from baseline
- Change in Norfolk QOL-DN from baseline

Exploratory Endpoints Include

- NT-proBNP
- Echo parameters
- Technetium (select sites only, change from baseline)

HELIOS-A Phase 3 study
now initiated

HELIOS-B Phase 3 outcomes study for ATTR* cardiomyopathy expected to initiate in
late 2019

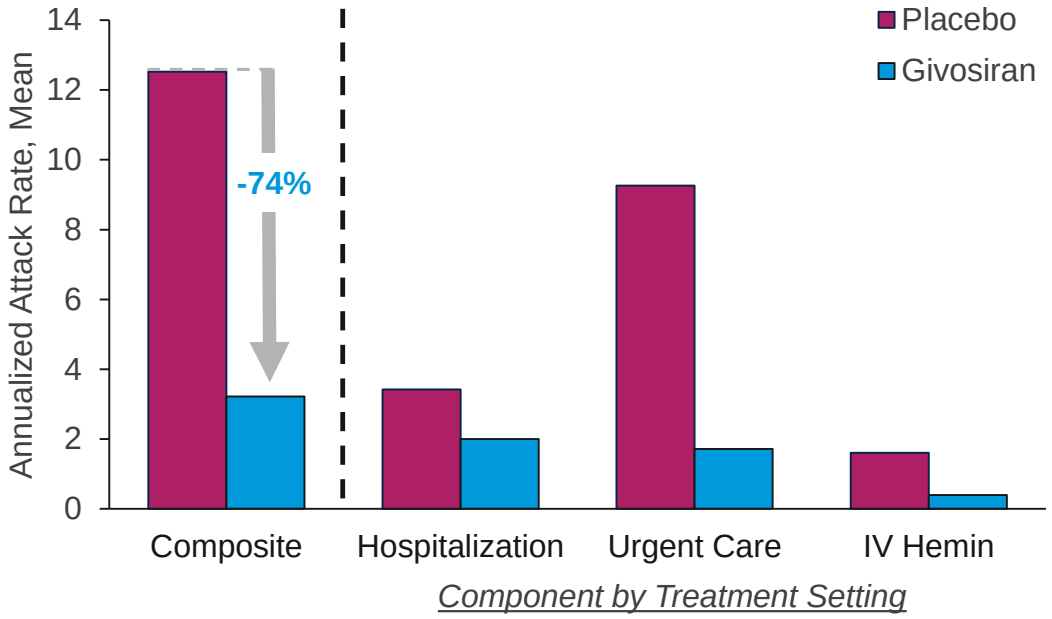
^ Primary endpoint for the study is at 9 months
* ATTR amyloidosis – wild-type or any TTR mutation

Givosiran ENVISION Phase 3 Study

Primary Efficacy Endpoint: Annualized Attacks in AIP

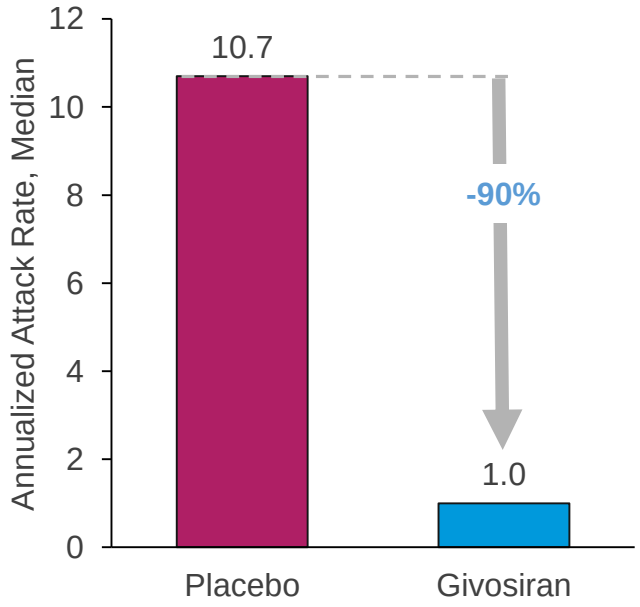
Primary Endpoint	Givosiran (N=46)	Placebo (N=43)	Rate Ratio (95% CI) (givosiran vs. placebo)	P-Value
Composite Annualized Attack Rate, Mean	3.2 (2.25, 4.59)	12.5 (9.35, 16.76)	0.26 (0.16, 0.41)	6.04×10^{-9}

Composite and all endpoint components reduced

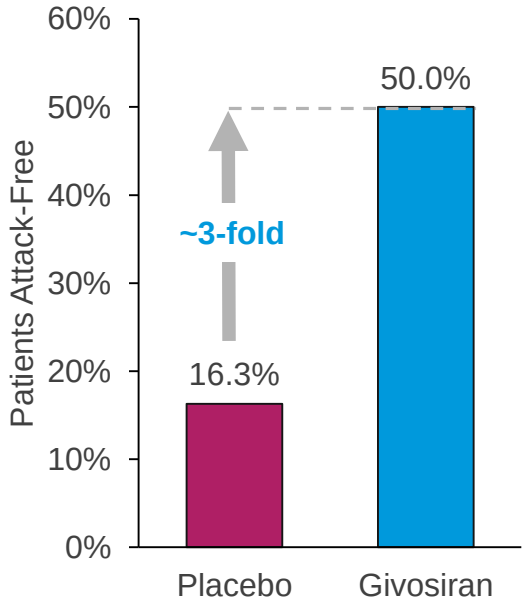


Component by Treatment Setting

Reduction in median composite attack rate



Increase in patients attack-free



Givosiran ENVISION Phase 3 Study

Safety Results

Safety	Givosiran (N = 48) n (%)	Placebo (N = 46) n (%)
Adverse Events (AEs)	43 (89.6%)	37 (80.4%)
Serious Adverse Event	10 (20.8%)	4 (8.7%)
Deaths	0 (0.0%)	0 (0.0%)
Discontinuations Due to AEs	1 (2.1%)	0 (0.0%)

- **Common AEs (>10% in either arm)**
  - More common in givosiran than placebo: nausea, injection site reaction, chronic kidney disease, fatigue
  - More common in placebo than givosiran: headache, vomiting, urinary tract infection, pyrexia
  - The AEs of chronic kidney disease were reported in five givosiran-treated patients (10.4 percent) and no placebo patients
    - 4 of 5 patients had prior history of CKD or a baseline eGFR < 60 mL/min/1.73m^2
    - Reductions in eGFR were early, asymptomatic and with evidence of reversibility; no patients had clinically significant proteinuria
    - No discontinuations due to renal AEs
- **ALT increases ≥3x ULN or baseline were observed in 7/48 (14.6%) patients on givosiran and 1/46 (2.2%) patients on placebo**
  - Majority of ALT elevations mild to moderate in severity; occurred after the first 3 to 5 doses of givosiran
  - One givosiran-treated patient discontinued due to ALT>8x ULN, a protocol-defined stopping rule; the elevation subsequently resolved (previously reported)
  - In remaining 6 givosiran-treated patients, peak ALT levels ranged from 3.0-5.4x ULN and were not accompanied by bilirubin increases. Patients were asymptomatic, and all events resolved with continued dosing (n=5) or after a brief pause in dosing (n=1)
- **No cases of anaphylaxis or pancreatitis**

As of April 2019

† Attacks requiring hospitalization, urgent healthcare visit, or hemin administration

* Endpoints evaluated in genetically-confirmed AIP patients, unless otherwise noted

Lumasiran ILLUMINATE•A Phase 3 Study

Randomized, Double-Blind Study in Primary Hyperoxaluria Type 1 Patients

N = 30
Patient Population

- Adults & children ≥6 years
- Urinary oxalate excretion ≥0.7 mmol/24hr/1.73m^2
- Confirmed alanine glyoxalate aminotransferase (*AGXT*) mutations
- eGFR >45 mL/min/1.73m^2

2:1 RANDOMIZATION

Lumasiran
3xqM loading dose, then q3M
3.0 mg/kg SC†

or

Placebo
3xqM loading dose, then q3M SC

Primary Endpoint

- Percent change in 24-hour urinary oxalate excretion at 6 months

Open-Label Extension

ILLUMINATE•A

FDA Breakthrough and EMA PRIME Designations

Topline ILLUMINATE-A results expected in **late 2019**

ILLUMINATE-C expected to initiate in **mid-2019**

NDA submission planned in **early 2020** (assuming positive results)

Topline ILLUMINATE-B results expected in **mid-2020**

† 3.0 mg/kg once monthly for 3 consecutive months (loading dose phase) followed by 3.0 mg/kg once every 3 months (maintenance phase) starting 1 month after last loading dose
ILLUMINATE-B: global Phase 3 pediatric study in patients under six years of age; ILLUMINATE-C: single-arm, open-label study in patients with impaired renal function

Other Clinical and Late Pre-Clinical Programs

Large Number of Additional Programs Across Orphan and Prevalent Diseases

PROGRAM	INDICATION	PREVALENCE	STAGE	EXPECTED MILESTONE	PARTNER
Inclisiran	*Hypercholesterolemia*	**~31 million** in U.S. with LDL-C levels >240 mg/dl	**Phase 3**	**2019** topline results	The Medicines Company
Fitusiran	*Hemophilia and Rare Bleeding Disorders*	**~200,000** worldwide	**Phase 3**	**2019** support Sanofi	SANOFI
Cemdisiran	*Complement-Mediated Diseases*	**>100,000** total complement-mediated diseases	**Phase 2**	**2019** advance Phase 2 IgA nephropathy study	REGENERON
Cemdisiran/ Pozelimab Combo	*Complement-Mediated Diseases*	**>100,000** total complement-mediated diseases	**Phase 1 planned**	**2019** advance combo studies	REGENERON
ALN-AAT02	*Alpha-1 Liver Disease*	**~12,000** worldwide	**Phase 1/2**	**Late 2019** initial Phase 1/2 data	Alnylam PHARMACEUTICALS
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*	**~400 million** worldwide with chronic disease	**Phase 1/2**	**Late 2019** initial Phase 1/2 data	VIR
ALN-AGT	*Hypertension*	**~9.1 million** in U.S. with resistant Hypertension	**Phase 1**	**Late 2019** initial Phase 1 data	Alnylam PHARMACEUTICALS

Alnylam-Regeneron Alliance*

Landmark Alliance Focused on CNS & Ocular RNAi Therapeutics

- Partnership of two leading biopharmaceutical companies committed to innovation
  - Alnylam R&D expertise and scientific excellence in RNAi therapeutics with emerging global commercial presence
  - Regeneron scientific excellence, world-leading capabilities in human genetics, and industry-leading commercial presence in ophthalmology and other large markets
- Broad, multi-product alliance across CNS, ocular, and select liver targets
  - Both companies fully participate in value creation with 50-50 structure in CNS and select liver programs
  - Milestone/royalty structure for ocular disease programs
- Accelerates Alnylam CNS and ocular programs, driving significant pipeline expansion
  - Robust, highly durable, and widely distributed RNAi knockdown of key targets in CNS/ocular pre-clinical models
  - Adds 1-2 new planned INDs/year toward CNS or ocular targets to previously planned 1-2 new INDs/year in liver beginning in 2020
- Significantly bolsters Alnylam balance sheet to >$2B *pro forma* for increased pipeline investment and future growth

* Alliance and equity agreements with Regeneron expected to close during Q2 2019

Barry Greene
President

Commercial/Med Affairs Highlights

ONPATTRO® Global Launch Update: Q1 2019

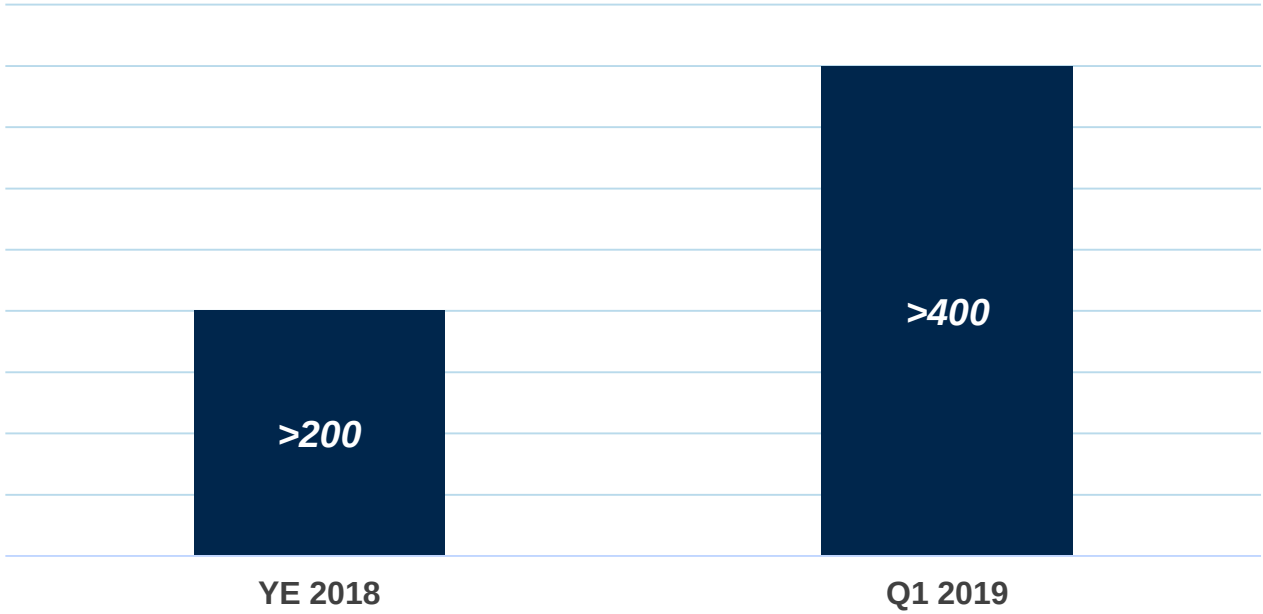
Strong Performance with Significant Growth Potential

$26.3M

ONPATTRO Global Q1
Net Product Revenues

>400

Patients Worldwide on Commercial
ONPATTRO at Q1 2019

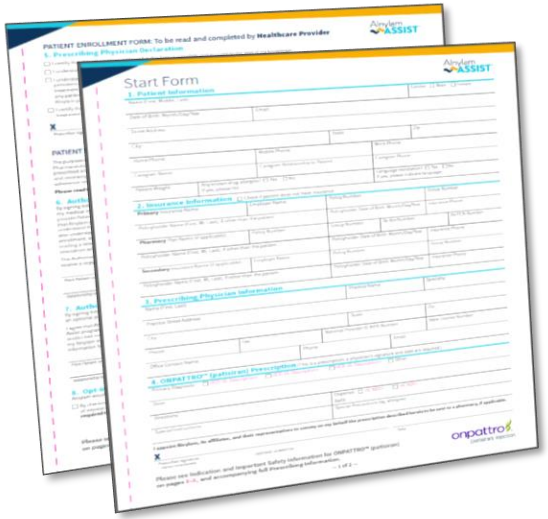


U.S. ONPATTRO Demand, Prescriber Trends, and Market Access

Q1 Metrics Based on 77 Start Forms

Patients

90% Non-EAP	10% EAP



Prescribers

55% Cardiology	35% Neurology	10% Other

>150 Physicians prescribing ONPATTRO since launch

~2 per week Average rate of new prescribers submitting Start Forms

Payers

65% Medicare	35% Other

10 VBAs in place with U.S. commercial payers

>90% U.S. lives with confirmed access to ONPATTRO*

Start Forms are an incomplete picture of U.S. demand (U.S. vial demand of 20-25% outside Alnylam Assist Channel); * DKP PayerScope® August 1, 2018 through March 31, 2019

EAP: Expanded Access Program; VBA: Value-Based Agreement

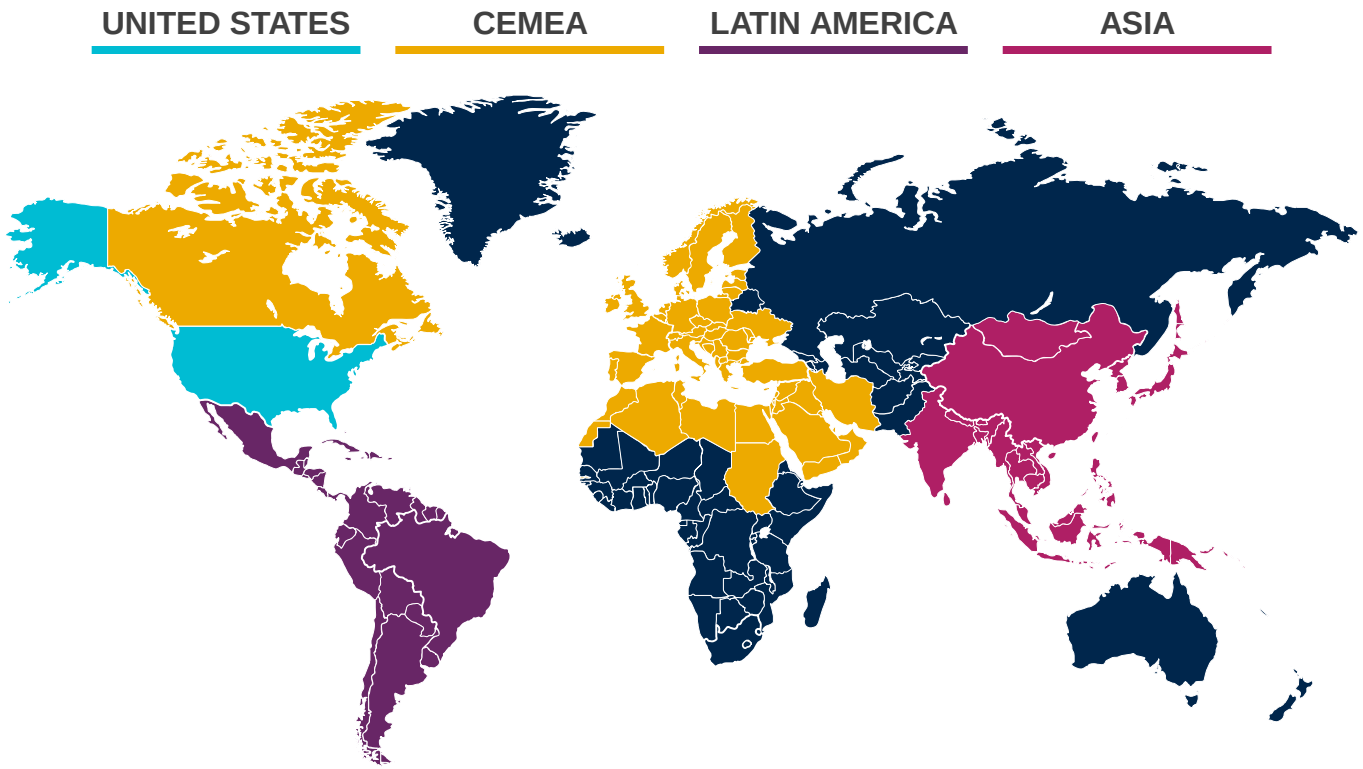
ONPATTRO Global Commercialization

Increasing Access and Value Recognition

- Significant progress with EU ONPATTRO availability outside EAP
  - Germany, France, Spain, the Netherlands, Luxembourg, Portugal, Sweden, Switzerland, and Austria

- Favorable HTA ratings underscore value proposition
  - France: ONPATTRO as only product in hATTR amyloidosis with ASMR III and ISP ratings
  - Germany: ONPATTRO as only product in hATTR amyloidosis with “considerable benefit” rating from Joint Federal Committee
  - Netherlands: agreement to reimburse ONPATTRO through joint negotiations coordinated by Zorgverzekeraars Nederland, Dutch Association of Health Insurers

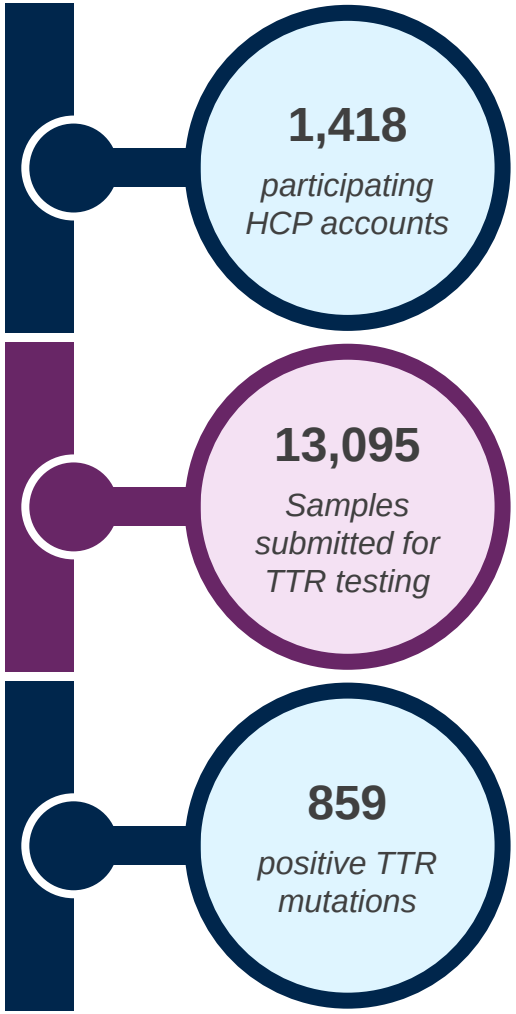
- Additional countries and regions advancing
  - Preparing for launch in Canada, following regulatory approval (expected mid-2019)
  - Perparing for launch in Japan, following regulatory approval (expected mid-2019)
  - Latin America plans under way, starting in Brazil



CEMEA: Canada, Europe, Middle East, North Africa; EAP: Expanded Access Program.

Alnylam Act

No-Charge, Third-Party Genetic Testing and Counseling Program



Reduce barriers to genetic testing and counseling to help people make more informed decisions about their health

Tests and services are performed by independent third parties

Available in U.S. and Canada (genetic counseling service available in U.S.)

Healthcare professionals who use this program have **no obligation** to recommend, purchase, order, prescribe, promote, administer, use or support any Alnylam product

More information regarding this program available at: **www.alnylamact.com**

Data as of April 2019

At no time does Alnylam receive patient-identifiable information. Alnylam receives contact information for healthcare professionals who use this program.

Givosiran Market Opportunity

Ultra-Rare Orphan Disease with Significant Disease Burden and Essentially No Competition

PREVALENCE

~1,000 *recurrent attacks*

~5,000 *sporadic attacks*

patients in U.S./EU[1]

DIAGNOSIS

~20%

currently diagnosed;
delays up to 15 years

DISEASE BURDEN

65%

recurrent attack patients
with chronic symptoms[2]

COST BURDEN

$400–650K

average annual expenditure,
recurrent attack patients[3]

GIVOSIRAN | ACUTE HEPATIC PORPHYRIA

>$500M potential market opportunity

[1] ORPHANET; The Porphyrias Consortium
[2] Gouya et al. EASL 2018
[3] EXPLORE Natural History Study (includes patients with ≥ 3 attacks per year). Annual expenditure per patient; based on both hospitalization charges (amount billed) and costs (amount paid) from published data sources in U.S.

Manmeet Soni
Chief Financial Officer

Financial Summary and Guidance

Financial Summary and Guidance

Financial Results	Q1 2019	Q1 2018
ONPATTRO Net Product Revenues	$26.3M	*n/a*
Total Revenues	$33.3M	$21.9M
Total GAAP Operating Costs and Expenses	$222.1M	$169.3M
• *R&D Expenses*	*$129.1M*	*$96.9M*
• *SG&A Expenses*	*$89.6M*	*$72.4M*
• *Cost of Goods Sold*	*$3.3M*	*n/a*
Non-GAAP Expenses		
• *Non-GAAP R&D Expenses**	*$113.0M*	*$86.7M*
• *Non-GAAP SG&A Expenses**	*$73.7M*	*$63.0M*
GAAP Net Loss	$181.9M	$141.2M
Non-GAAP Net Loss**	$149.9M	$121.6M

First Quarter 2019 Cash & Shares

- Cash $1.29B
  - Includes $44.8M in restricted investments
  - >$2B *pro-forma* cash upon Regeneron closing
- Shares Outstanding 106.4M

2019 Financial Guidance

- Annual Non-GAAP Operating Expenses:
  - Non-GAAP R&D Expenses* in the range of $550M to $590M
  - Non-GAAP SG&A Expenses* in the range of $390M to $410M
- Current cash, cash equivalents, and marketable debt securities expected to support company operations for multiple years based on current operating plan

* Non-GAAP operating expenses exclude stock-based compensation expenses.
** Non-GAAP net loss excludes stock-based compensation expenses.
See Appendix for a reconciliation between GAAP and non-GAAP measures.

Yvonne Greenstreet, MBChB, MBA
Chief Operating Officer

2019 Goals Update

Alnylam 2019 Goals

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

		2019*		
		Early	Mid	Late
onpattro (patisiran) lipid complex injection 10 mg/5 mL (ATTR Amyloidosis)	Commercial Execution	✓	●	●
	Japan Launch			●
	Additional Country Launches	✓	●	●
	Start APOLLO-B Cardiomyopathy Phase 3		●	
VUTRISIRAN (ATTR Amyloidosis)	HELIOS-A Polyneuropathy Phase 3 Enrollment	✓	●	●
	Start HELIOS-B Cardiomyopathy Phase 3			●
GIVOSIRAN (Acute Hepatic Porphyria)	ENVISION Phase 3 Topline Results	✓		
	File NDA		●	
	File MAA		●	
LUMASIRAN (Primary Hyperoxaluria Type 1)	Complete ILLUMINATE-A Phase 3 Enrollment		●	
	ILLUMINATE-A Phase 3 Topline Results			●
	Start ILLUMINATE-B & C Phase 3 Studies	✓	●	
ADDITIONAL CLINICAL PROGRAMS	Continue to advance early/mid-stage pipeline; File new INDs; Present clinical data	✓	●	●
PARTNERED PROGRAMS				
INCLISIRAN (Hypercholesterolemia)	ORION-9, 10, & 11 Phase 3 Topline Results		●	●
	File NDA			●
FITUSIRAN (Hemophilia and RBD)	Support Sanofi on ATLAS Phase 3	✓	●	●

Q1 2019 Financial Results

Q&A Session

Alnylam PHARMACEUTICALS

Q1 2019 Financial Results

Appendix

Alnylam Pharmaceuticals, Inc.

Reconciliation of Selected GAAP Measures to Non-GAAP Measures

(In thousands, except per share amounts)

	Three Months Ended March 31,	
	2019	2018
Reconciliation of GAAP to Non-GAAP Research and development:		
GAAP Research and development	$ 129,127	$ 96,857
Less: Stock-based compensation expenses	(16,125)	(10,137)
Non-GAAP Research and development	$ 113,002	$ 86,720
Reconciliation of GAAP to Non-GAAP Selling, general and administrative:		
GAAP Selling, general and administrative	$ 89,608	$ 72,447
Less: Stock-based compensation expenses	(15,907)	(9,447)
Non-GAAP Selling, general and administrative	$ 73,701	$ 63,000
Reconciliation of GAAP to Non-GAAP Operating costs and expenses:		
GAAP Operating costs and expenses	$ 222,082	$ 169,304
Less: Stock-based compensation expenses	(32,032)	(19,584)
Non-GAAP Operating costs and expenses	$ 190,050	$ 149,720
Reconciliation of GAAP to Non-GAAP Net loss:		
GAAP Net loss	$ (181,915)	$ (141,214)
Add: Stock-based compensation expenses	32,032	19,584
Non-GAAP Net loss	$ (149,883)	$ (121,630)
Reconciliation of GAAP to Non-GAAP Net loss per common share-basic and diluted:		
GAAP Net loss per common share - basic and diluted	$ (1.73)	$ (1.41)
Add: Stock-based compensation expenses	0.31	0.19
Non-GAAP Net loss per common share - basic and diluted	$ (1.42)	$ (1.22)