# Fourth Quarter and Full Year 2018 Financial Results

**February 7, 2019**

Alnylam® PHARMACEUTICALS

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# Agenda

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

**Q4 2018 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**
- John Maraganore, Ph.D.
  Chief Executive 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 report on Form 10-Q 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

# Q4 2018 Overview

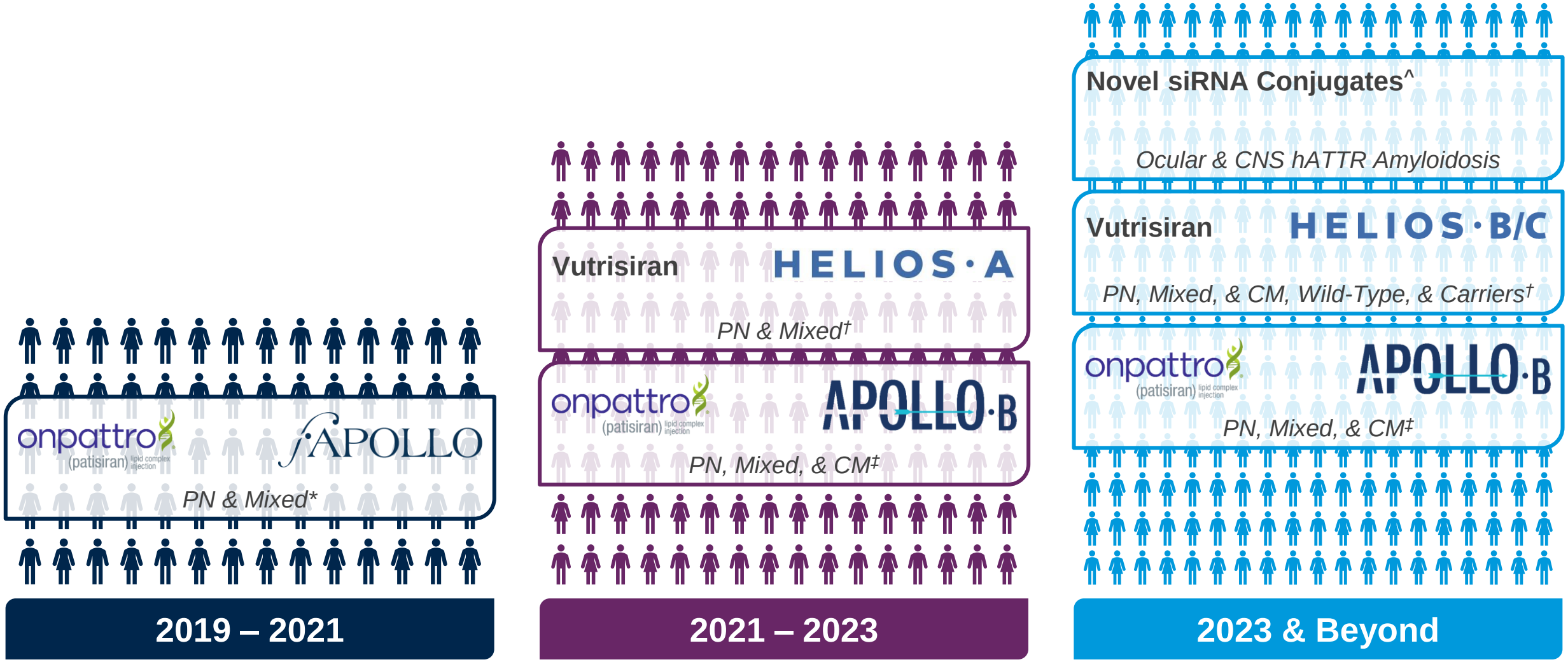
# The first RNAi therapeutic is NOW APPROVED

onpattro®
(patisiran) lipid complex injection

onpattro®
2 mg/mL concentrate for solution for infusion patisiran

# Alnylam ATTR Amyloidosis Franchise

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




* ONPATTRO is approved in the U.S. for the treatment of the polyneuropathy of hATTR amyloidosis in adults, and in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; ‡ ONPATTRO has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population; † Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; ^ Novel siRNA conjugate development candidates for ocular or CNS hATTR amyloidosis not yet selected.

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

# Beyond ONPATTRO: Multiple Launches Planned in Next 2-3 Years

| 2018 | 2019-2021 | | | Partnered programs*: 2020-2021 | |
|---|---|---|---|---|---|
| onpattro (patisiran) lipid complex injection | Givosiran | Lumasiran | Vutrisiran | Fitusiran | Inclisiran |
| ONPATTRO is indicated in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults^ | Acute hepatic porphyria | Primary hyperoxaluria type 1 | ATTR amyloidosis | Hemophilia | Hypercholesterolemia |


Robust pipeline and global commercial infrastructure support sustainable product launches ***beyond 2021***

* Sanofi Genzyme is leading and funding development of fitusiran and will commercialize program, if successful;
The Medicines Company is leading and funding development of inclisiran and will commercialize program, if successful
^ ONPATTRO is approved in the EU for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy
Anticipated dates of launch based on current development timelines for investigational therapeutics and assuming positive pivotal study data and regulatory approval

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


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 cardiomyopathy expected to initiate in **late 2019**



^ Primary endpoint for the study is at 9 months

# Givosiran ENVISION Phase 3 Study

## Randomized, Double-Blind, Placebo-Controlled Study in Acute Hepatic Porphyria (AHP) Patients

### Enrollment completed – 94 AHP patients, 36 sites, 18 countries

**Patient Population**

- Age ≥12 years
- Diagnosis of AHP
- ≥2 attacks within prior 6 months

1:1 RANDOMIZATION

**Givosiran** SC qM 2.5 mg/kg

or

**Placebo** SC qM

**Primary Endpoint**

- Attacks requiring hospitalization, urgent care visit, home IV hemin at 6 months

**Open-Label Extension**

ENVISION

**FDA Breakthrough and EMA PRIME Designations**

**Interim efficacy analysis (ALA levels at 3 months in AIP patients)**

- Statistically significant reduction in urinary ALA, relative to placebo ($p < 0.001$)

**Interim safety**

- No deaths
- Serious Adverse Events (SAE) reported in:
  - 5/23 (22%) of patients on givosiran
  - 2/20 (10%) of patients on placebo
- One patient (4%) on givosiran discontinued treatment based on a protocol-defined stopping rule due to >8x ULN increase in liver transaminase, which resolved
- No treatment discontinuations in placebo group

Topline ENVISION results expected in **early 2019**



AIP: Acute Intermittent Porphyria; Data cut-off date of August 22, 2018 for all interim data and included 41 patients with AIP, one with variegate porphyria, and one with hereditary coproporphyria who were on study for at least three months

# Givosiran Phase 1 Results Published in *The New England Journal of Medicine*


February 7, 2019
N Engl J Med 2019; 380:549-558
DOI: 10.1056/NEJMoa1807838

# 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-B & -C expected to initiate in **mid-2019**

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

† 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

# 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** initiate Phase 2 IgA nephropathy study | Alnylam PHARMACEUTICALS |
| **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 | **Preclinical** | **2019** IND/CTA filings | Alnylam PHARMACEUTICALS |



* Subject to Sanofi option rights

# RNAi Therapeutics for CNS and Ocular Diseases

## Expand Alnylam Opportunities Beyond Liver

### Devastating diseases with enormous burden and unmet need

- Alzheimer's disease
- Amyotrophic lateral sclerosis (ALS)
- Cerebral amyloid angiopathy
- Frontotemporal dementia
- Huntington's disease
- Multi-system atrophy
- Parkinson's disease
- Spinocerebellar ataxia

- AMD, dry
- AMD, wet
- Birdshot chorioretinopathy
- Dominant retinitis pigmentosa 4
- Fuch's dystrophy
- hATTR amyloidosis
- Hereditary and sporadic glaucoma
- Stargardt's disease

### RNAi therapeutics demonstrate potent, widely distributed, and highly durable effects

## ALN-APP

**Targeting amyloid precursor protein (APP) for hereditary cerebral amyloid angiopathy (hCAA)**

- hCAA caused by APP mutations leading to arteriolar Aβ deposition with microbleeds and intracranial hemorrhages
- Multiple CSF and radiologic biomarkers for early readout
- Study of hCAA potential gateway to larger indications (e.g., sporadic CAA, EOFAD, AD)

1st IND expected in **late 2019/early 2020**

1-2 INDs/year planned starting in **2020**

Barry Greene
President

# Commercial/Med Affairs Highlights

# ONPATTRO Global Launch Update: Q4 2018

## Strong Performance with Significant Growth Potential

**$12.1M**

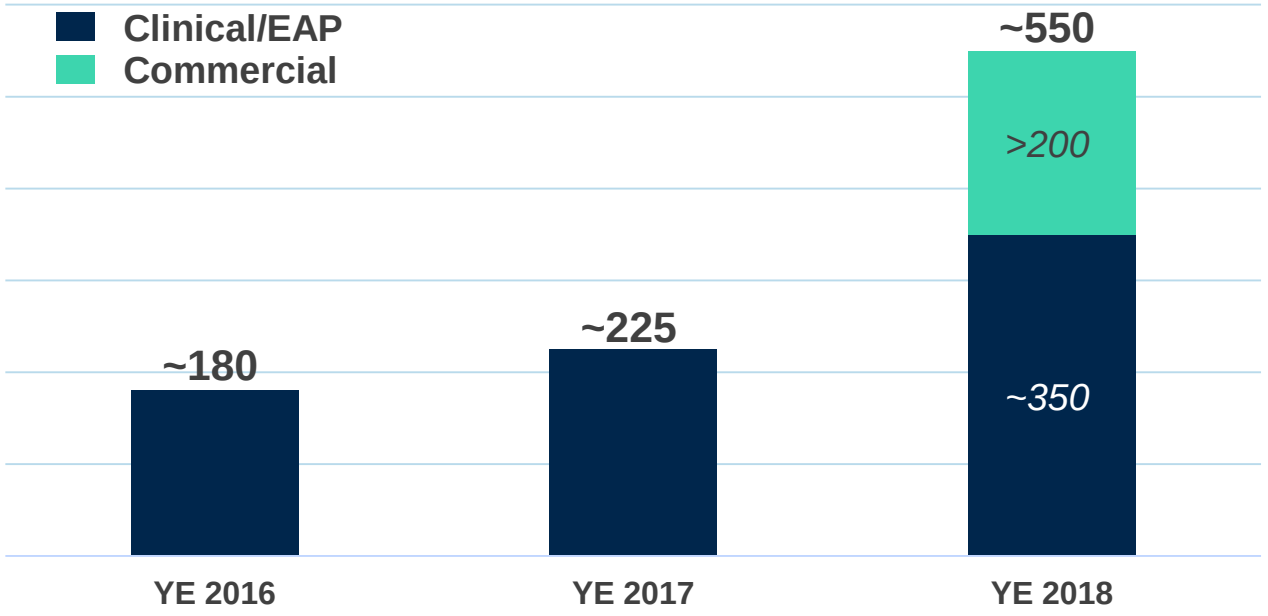
ONPATTRO Global Q4 Net Product Revenues


**>200**

U.S./EU Patients on Commercial ONPATTRO at YE 2018

**~550**

Total Global Patients on ONPATTRO/Patisiran at YE 2018



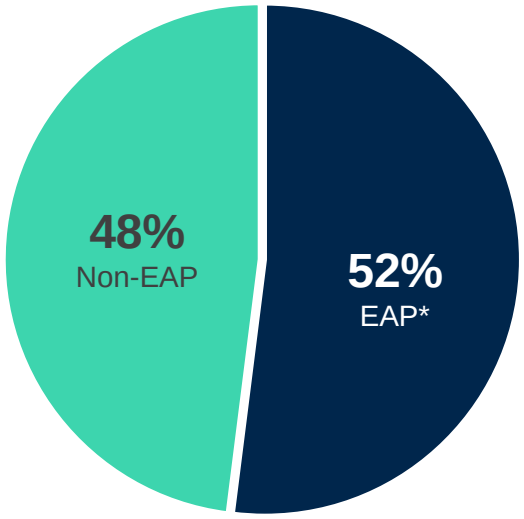
# U.S. ONPATTRO Demand and Prescriber Trends

## Broad Prescriber Base Driving Strong Patient Uptake

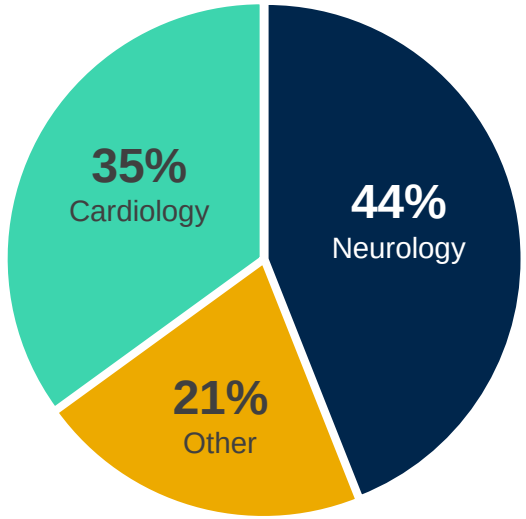

**250**

U.S. Start Forms
(Launch to YE 2018)

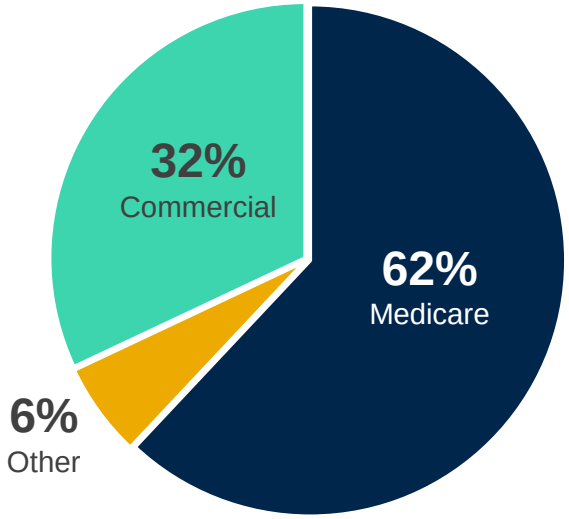
### Patient Source




### Prescribing Specialties




### Payer Mix

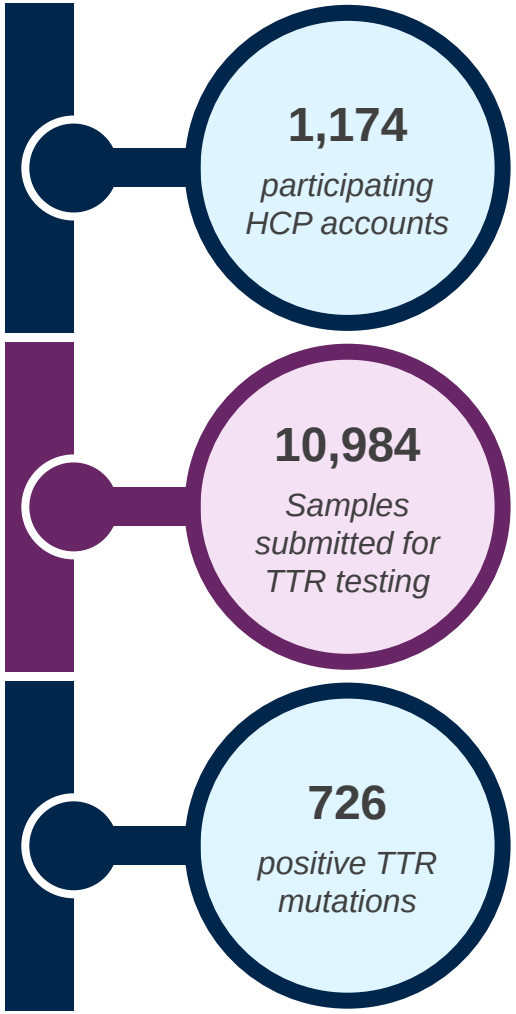





* Expanded Access Program

# 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 February 6, 2019

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

# ONPATTRO® (patisiran) can reverse polyneuropathy manifestations of the disease[1,2]

## A novel RNAi-based approach that may transform the future for your patients[1-4]

At 18 months in a placebo-controlled study, ONPATTRO demonstrated:

- Reversal in neuropathy impairment from baseline as measured by modified Neuropathy Impairment Score + 7 (mNIS+7)[1]
- Improvement in quality of life from baseline as measured by Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) score[1]
- Improvement in autonomic symptoms from baseline as measured by Composite Autonomic Symptom Score 31 (COMPASS 31)[2]
- Improvement in gait speed from baseline as measured by 10-meter walk test (10MWT)[1]

**Indication**

ONPATTRO® (patisiran) is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

**Important Safety Information**

**Infusion-Related Reactions**

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. Monitor for signs and symptoms during infusion. Slow or interrupt the infusion if clinically indicated. Discontinue the infusion if a serious or life-threatening infusion-related reaction occurs.

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

RNA=ribonucleic acid; RNAi=RNA interference.

**References: 1.** ONPATTRO [U.S. package insert]. **2.** Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. *N Engl J Med*. 2018;379(1):11-21 **3.** Ando Y, et al. *Orphanet J Rare Dis*. 2013;8:31. **4.** Adams D, et al. *Neurology*. 2015;85(8):675-682.

## Manmeet Soni
## Chief Financial Officer

# Financial Summary and Guidance

# Financial Summary and Guidance

| 2018 Financial Results | Q4 2018 | FY 2018 |
|---|---|---|
| ONPATTRO Net Product Revenues | $12.1M | $12.5M |
| Total GAAP Operating Costs and Expenses | $241.4M | $889.6M |
| • *R&D Expenses* | *$131.0M* | *$505.4M* |
| • *SG&A Expenses* | *$108.7M* | *$382.4M* |
| • *Cost of Goods Sold* | *$1.7M* | *$1.8M* |
| Non-GAAP Expenses | | |
| • *Non-GAAP R&D Expenses** | *$118.1M* | *$424.9M* |
| • *Non-GAAP SG&A Expenses** | *$93.7M* | *$305.1M* |
| GAAP Net Loss | $211.4M | $761.5M |
| Non-GAAP Net Loss** | $183.5M | $624.3M |

## 2018 Year End Cash & Shares

- Cash $1.13B
  - Includes $44.8M in restricted investments
  - ~$1.5B *pro-forma* cash post-January 2019 financing
- Shares Outstanding 101.2M
  - ~106.3M shares outstanding as of Jan. 31, 2019

## 2019 Financial Guidance

- Annual Non-GAAP Operating Expenses:
  - Non-GAAP R&D Expenses* in the range of $520M to $560M
  - Non-GAAP SG&A Expenses* in the range of $390M to $420M
- Current cash, cash equivalents, and marketable debt securities expected to support company operations for ~two years based on current operating plan

* Non-GAAP operating expenses exclude stock-based compensation expenses.
** Non-GAAP net loss excludes stock-based compensation expenses and for FY 2018 excludes the gain on litigation settlement.
See Appendix for a reconciliation between GAAP and non-GAAP measures.

## John Maraganore, Ph.D.
## Chief Executive 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 (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 | ● | ● | ● |

## Q4 and Full Year 2018 Financial Results

# Q&A Session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## Q4 and Full Year 2018 Financial Results

# Appendix

# Alnylam Pharmaceuticals, Inc.

## Reconciliation of Selected GAAP Measures to Non-GAAP Measures
## (In thousands, except per share amounts)

| | Three Months Ended December 31, | | Year Ended December 31, | |
|---|---|---|---|---|
| | 2018 | 2017 | 2018 | 2017 |
| **Reconciliation of GAAP to Non-GAAP Research and development:** | | | | |
| GAAP Research and development | $ 131,036 | $ 117,772 | $ 505,420 | $ 390,635 |
| Less: Stock-based compensation expenses | (12,972) | (14,837) | (80,509) | (51,872) |
| Non-GAAP Research and development | $ 118,064 | $ 102,935 | $ 424,911 | $ 338,763 |
| **Reconciliation of GAAP to Non-GAAP Selling, general and administrative:** | | | | |
| GAAP Selling, general and administrative | $ 108,688 | $ 67,455 | $ 382,359 | $ 199,365 |
| Less: Stock-based compensation expenses | (15,001) | (12,280) | (77,243) | (40,947) |
| Non-GAAP Selling, general and administrative | $ 93,687 | $ 55,175 | $ 305,116 | $ 158,418 |
| **Reconciliation of GAAP to Non-GAAP Operating costs and expenses:** | | | | |
| GAAP Operating costs and expenses | $ 241,389 | $ 185,227 | $ 889,581 | $ 590,000 |
| Less: Stock-based compensation expenses | (27,973) | (27,117) | (157,752) | (92,819) |
| Non-GAAP Operating costs and expenses | $ 213,416 | $ 158,110 | $ 731,829 | $ 497,181 |
| **Reconciliation of GAAP to Non-GAAP Net loss:** | | | | |
| GAAP Net loss | $ (211,441) | $ (142,227) | $ (761,497) | $ (490,874) |
| Add: Stock-based compensation expenses | 27,973 | 27,117 | 157,752 | 92,819 |
| Less: Gain on litigation settlement | — | — | (20,564) | — |
| Non-GAAP Net loss | $ (183,468) | $ (115,110) | $ (624,309) | $ (398,055) |
| **Reconciliation of GAAP to Non-GAAP Net loss per common share-basic and diluted:** | | | | |
| GAAP Net loss per common share - basic and diluted | $ (2.09) | $ (1.48) | $ (7.57) | $ (5.42) |
| Add: Stock-based compensation expenses | 0.27 | 0.28 | 1.57 | 1.02 |
| Less: Gain on litigation settlement | — | — | (0.21) | — |
| Non-GAAP Net loss per common share - basic and diluted | $ (1.82) | $ (1.20) | $ (6.21) | $ (4.40) |