First Quarter 2016 Financial Results

May 2, 2016

Alnylam® PHARMACEUTICALS

Agenda

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

Q1 2016 Overview
- John Maraganore, Ph.D.
  Chief Executive Officer

Alnylam Clinical Pipeline
- Pushkal Garg, M.D.
  Senior Vice President, Clinical Development

Financial Results
- Michael Mason
  Vice President, Finance and Treasurer

2016 Goal Update
- Barry Greene
  President and Chief Operating Officer

Q&A Session

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. 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, successfully demonstrate the efficacy and safety of our drug candidates, obtain, maintain and protect intellectual property, enforce our patents and defend our patent portfolio, obtain regulatory approval for products, establish and maintain business alliances; our dependence on third parties for access to intellectual property; and the outcome of litigation, 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.

John Maraganore, Ph.D.
Chief Executive Officer

Q1 2016 Overview

Pushkal Garg, M.D.
Senior Vice President, Clinical Development

Alnylam Clinical Pipeline

Alnylam ATTR Amyloidosis Portfolio

Committed to Continued Innovation for Patients

patisiran

hATTR-PN

- IV administration
- Phase 2 completed
- Phase 2 Open-Label Extension (OLE) study ongoing
- APOLLO Phase 3 trial ongoing; fully enrolled

revusiran

hATTR-CM

- SC administration
- Phase 2 completed
- Phase 2 OLE study ongoing
- ENDEAVOUR Phase 3 trial ongoing

ALN-TTRsc02

ATTR

hATTR-PN, hATTR-CM & wtATTR

- ESC “second generation” chemistry
- Expect quarterly SC dose regimen
- CTA filed March 2016; data expected late 2016
- Phase 3 start planned for 2017

Alnylam PHARMACEUTICALS

APOLLO Phase 3 Study Design

Enrollment Complete

N=225

Patient Population
- hATTR-PN: any TTR mutation, Stages 1 and 2
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

2:1 RANDOMIZATION

Patisiran IV q3W, 0.3 mg/kg

OR

Placebo IV q3W

Primary Endpoint at 18 months
- mNIS+7

Key Secondary Endpoints
- Norfolk QOL-DN
- NIS-weakness
- mBMI
- 10-meter walk

All completers eligible for patisiran treatment on Phase 3 OLE study (APOLLO-OLE)

Enrollment completed end of January, supporting 2017 NDA and MAA if study is positive

Statistical Considerations

- Placebo-estimated mNIS+7 progression rate of 17.8 points/year derived from natural history study of 283 hATTR-PN patients
- 90% Power to detect as little as 37.5% difference in ΔmNIS+7 between treatment groups with 2-sided alpha=0.05
  - Based on original target enrollment of 200 patients

Clinicaltrials.gov # NCT01960348

Alnylam PHARMACEUTICALS

Patisiran Interim Phase 2 OLE Study Results*

Ongoing Study in hATTR-PN Patients

Mean max **92%** TTR KD **clamped** thru 24 months

Neurological impairment **stabilized** at 18 months with mean **0.8** point **decrease** in mNIS+7

TTR KD correlated with **improvement** in **mNIS+7** scores

Median **77%** **increase** in sweat gland nerve fiber density on biopsy

Evidence for Potential Halting of Neuropathy Progression

Safety: Generally well tolerated out to 25 months

- 8 non-drug related SAEs in 5 patients
- Majority of AEs mild to moderate, including mild flushing (22.2%) and infusion-related reactions (18.5%)
- No significant lab findings, no drug-related discontinuations

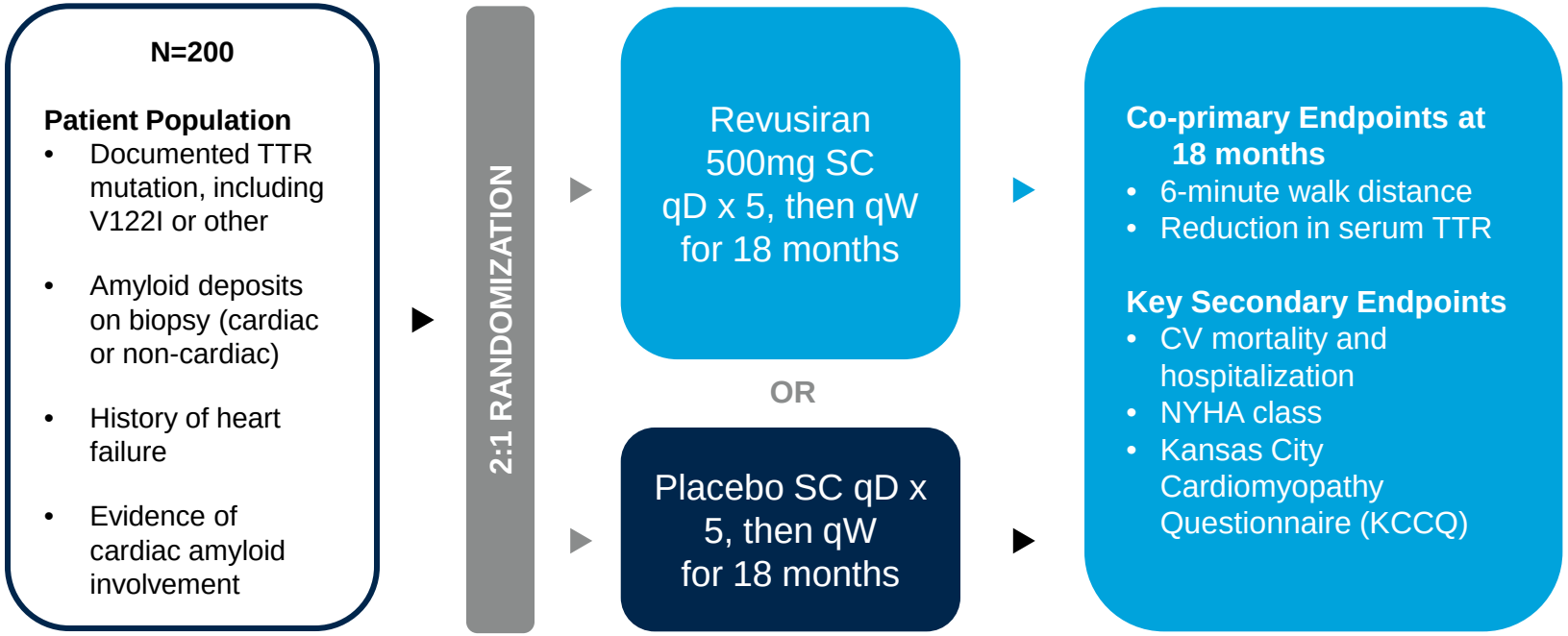
PLANNED NEXT STEPS

24-month Phase 2 OLE data in **mid-2016**

*Preliminary Phase 2 OLE results based on data in database as of February 23, 2016; Adams, *AAN*, April 2016

Alnylam PHARMACEUTICALS

ENDEAVOUR Phase 3 Study Design



All completers eligible for revusiran treatment on Phase 3 OLE study

Expect to complete enrollment in late 2016; Report data in mid-2018

Statistical Considerations

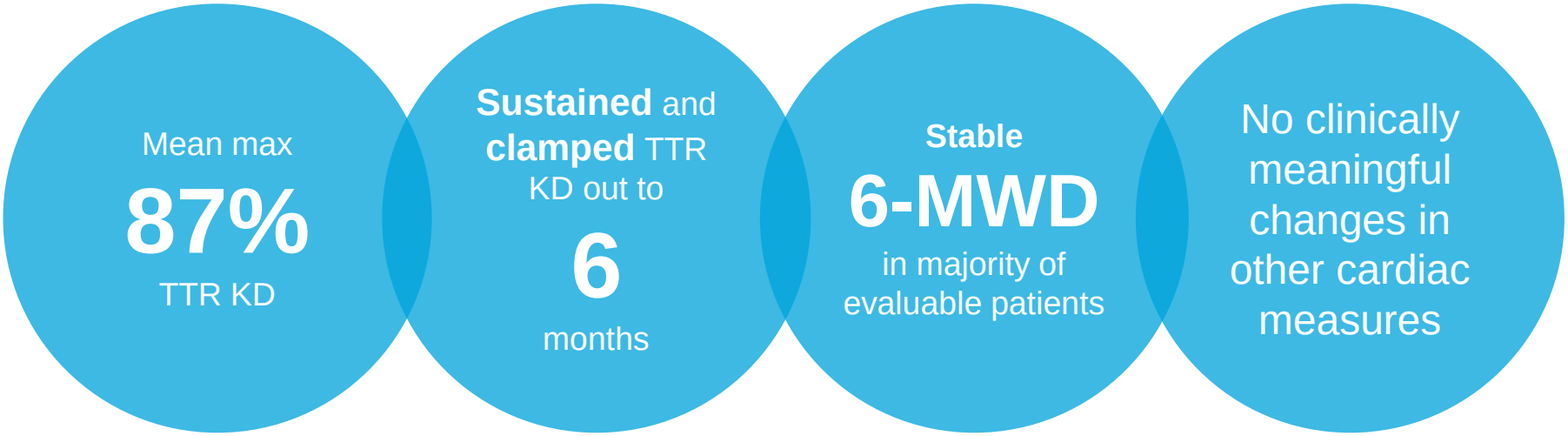
- Placebo-estimated decline in 6-MWD of ~140 meters over 18 months in natural history study of 137 hATTR-CM patients (N=39 for 6-MWD data)
- 90% Power to detect as little as 39% difference in 18 mo change from baseline 6-MWD between treatment groups with significance level of $p < 0.05$
- Unblinded interim analysis for futility when ~50% of patients reach 18 months

Clinicaltrials.gov # NCT02319005

Alnylam PHARMACEUTICALS

Revusiran Interim Phase 2 OLE Study Results*

Ongoing Study in hATTR-CM Patients



Opportunity to Evaluate Effects of TTR Knockdown in hATTR-CM

Safety: Generally well tolerated in majority of patients

- SAEs in 8 patients (32%), including one death due to infiltrative cardiomyopathy; all SAEs deemed not related to drug
- Majority of AEs mild or moderate
- Injection site reactions (ISRs) reported in 11 patients (44%)
  - 3 discontinuations due to ISRs or diffuse rash; no further discontinuations due to ISRs at last reporting date
- Reversible LFT elevation in 1 patient resulting in dose reduction; no other notable lab abnormalities

PLANNED NEXT STEPS

12-month Phase 2 OLE data in **mid-2016**

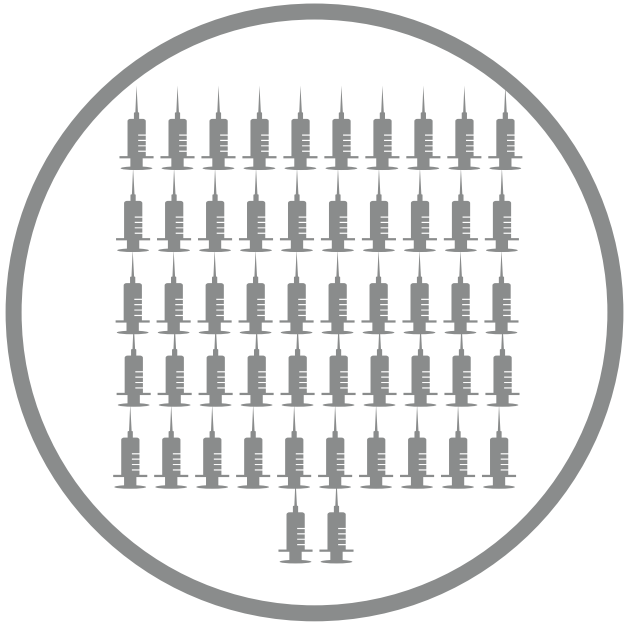
*Preliminary Phase 2 OLE results as of October 13, 2015; Gilmore, *EC-ATTR*, November 2015

Alnylam PHARMACEUTICALS

ALN-TTRsc02 Opportunity

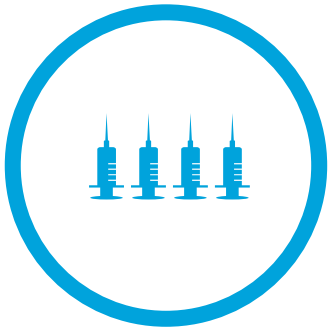
Potential for Best-in-Class Profile

Revusiran/IONIS-TTR$_{Rx}$



52 DOSES PER YEAR

ALN-TTRsc02



4 DOSES PER YEAR ANTICIPATED

PLANNED NEXT STEPS

CTA filed	**Phase 1 start**	**Initial Data**	**Phase 3 start**
in March 2016	mid-2016	late 2016	in 2017

Fitusiran Interim Phase 1 Study Results*

Ongoing Study in Hemophilia A & B Patients

Up to **88%** AT lowering

Up to **mean 285%** increase in thrombin generation

85-92% Reduction in median estimated ABR

No thrombotic events/ no significant D-dimer increases

DURABILITY

Monthly SC dose regimen

Evidence for Potential Restoration of Hemostasis in Severe Hemophilia A and B

Safety: Generally well tolerated

- No SAEs; majority of AEs mild or moderate, and transient; no discontinuations
- Mild, transient ISRs in 2 (8%) patients

PLANNED NEXT STEPS

Additional data
in **mid- and late 2016**

Start Phase 3 studies
in **mid- and late 2016**

*Preliminary Phase 1 study results as of November 12, 2015; Pasi *et al.*, *ASH*, December 2015

Alnylam PHARMACEUTICALS

ALN-CC5 Initial Phase 1/2 Study Results*

Ongoing Study in Healthy Volunteers and PNH Patients

Up to **99%** C5 KD

Nadir residual C5 less than **1 mcg/mL**

Clamped PD for over **90** days after **single** dose

Mean max inhibition of sheep RBC hemolytic activity up to **84%**

DURABILITY

Monthly and possibly **quarterly** SC dose regimen for eculizumab poor responders and eculizumab sparing

Significant and Durable Knockdown of Serum C5 Drives Opportunity to Address Eculizumab Limitations in PNH

Safety: Generally well tolerated

- All AEs mild or moderate in severity; no SAEs, no discontinuations
- Mild, transient ISRs observed in 6 (18.75%) subjects

PLANNED NEXT STEPS

Data in ~5 PNH patients
on **June 11** at **EHA**

Start PNH Phase 2
in **late 2016**

*Preliminary Phase 1 study results as of October 19, 2015 or November 6, 2015; Sorensen, *ASH*, December 2015

Alnylam PHARMACEUTICALS

ALN-AS1 Initial Phase 1 Study Results*

Ongoing Study in Asymptomatic & Symptomatic Porphyria Patients

DURABILITY

Monthly and possibly **quarterly** SC dose regimen

Potent, Dose-Dependent Lowering of Toxic Heme Intermediates that Mediate Attacks

Safety: Generally well tolerated

- No SAEs related to study drug and no discontinuations
- All AEs reported were mild-moderate in severity
- No clinically significant laboratory abnormalities related to study drug

PLANNED NEXT STEPS

Recurrent attack patient data
in **late 2016**

Start Phase 3
in **2017**

*Preliminary Phase 1 study results as of September 2, 2015; Sardh *et al.*, *ICPP*, December 2015

Alnylam PHARMACEUTICALS

Primary Hyperoxaluria Type 1 (PH1)
ALN-GO1

DESCRIPTION

Genetic mutations lead to excessive oxalate production, resulting in recurrent kidney stones and extensive renal damage

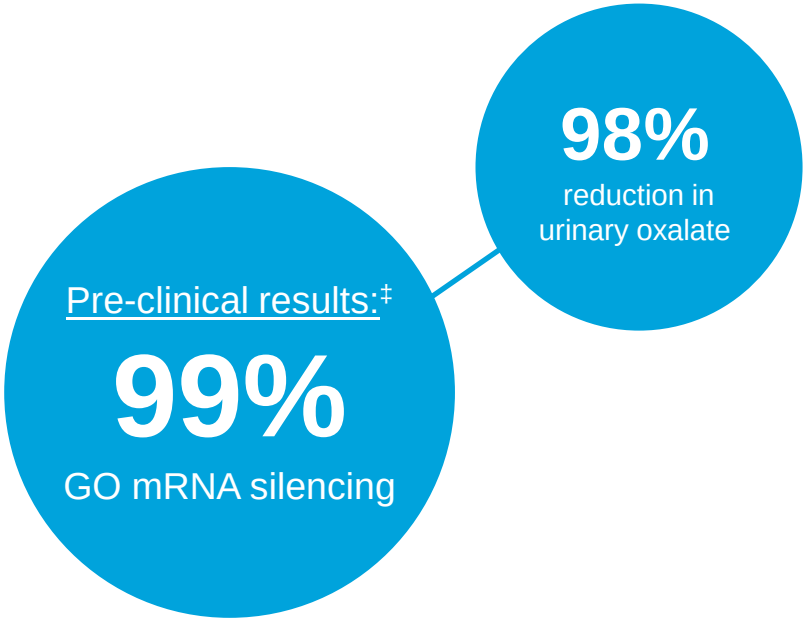
PATIENT POPULATION*

~5,000
worldwide

Leads to **renal failure** in **children**

DRUG MECHANISM

ALN-GO1 targets glycolate oxidase (GO), an enzyme upstream from the genetic defect, for potential lowering of oxalate levels



Phase 1 initiated
in **March 2016**

PLANNED NEXT STEPS

Initial clinical data
in **late 2016**

* Cochat *et al., N Engl J Med,* 2013
‡ Erbe, *ESPN, September 2015*

Alnylam PHARMACEUTICALS

ALN-PCSsc ORION-1 Phase 2 Study*

480 ASCVD subjects with elevated LDL-C on maximal lipid lowering therapy

The Orion Program

Primary objectives

- LDL-C levels at day 180

Secondary objectives

- Safety and tolerability, PCSK9 and LDL-C reduction and duration of effect qQ vs Bi-annual, proportion of patients reaching global lipid guidelines, changes in other lipoprotein levels

Randomized 3:1, Double blind, Placebo controlled

*The Medicines Company is leading and funding development of the ALN-PCSsc program from Phase 2 onward and will commercialize the program, if successful

The Medicines Company

Alnylam PHARMACEUTICALS

Hepatitis B Virus (HBV) Infection
ALN-HBV

DESCRIPTION

Viral infection leading to cirrhosis and hepatocellular carcinoma (HCC)

PATIENT POPULATION*

1/3 of world population infected

400M patients worldwide, **25M** in U.S./EU with chronic infection

DRUG MECHANISM

ALN-HBV targets all four transcripts of viral genome for potential reduction of HBsAg levels and increase in seroconversion rates

Pre-clinical results:‡

up to **3.6** $\log_{10}$ HBsAg reduction

>4 $\log_{10}$ reduction in viral DNA in chronically infected chimps

CTA filed in **February 2016**

PLANNED NEXT STEPS

Phase 1 Start in **mid-2016**

* WHO; *Global Data Report*, 2015
‡ Sepp-Lorenzino, *Liver Meeting,* November 2015

Alnylam PHARMACEUTICALS

Michael Mason

Vice President, Finance and Treasurer

Q1 2016 Financial Results

Financial Summary and Guidance

2016 Q1 Financial Results

- Cash ~$1.21B
- GAAP Revenues $7.3M
- Total GAAP Operating Expenses $117.4M
  - Research and Development Expense $96.3M
  - General and Administrative Expense $21.1M
- GAAP Net Loss of $103.0M
- Shares Outstanding ~85.5M

2016 Guidance

- Year-end cash >$1.0B
  - Includes $150 million of restricted marketable securities received from credit agreements related to build out of new drug substance manufacturing facility

Barry Greene

President and Chief Operating Officer

2016 Goals Update

Alnylam 2016 Pipeline Goals

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

		2016*		
		Early	Mid	Late
PATISIRAN (Hereditary ATTR Amyloidosis with Polyneuropathy)	Complete APOLLO Phase 3 Accrual	✓		
	Phase 2 OLE 24 Month Data		●	
REVUSIRAN (Hereditary ATTR Amyloidosis with Cardiomyopathy)	Complete ENDEAVOUR Phase 3 Accrual			●
	Phase 2 OLE 12 Month Data		●	
ALN-TTRsc02 (ATTR Amyloidosis)	CTA Filing	✓		
	Start Phase 1		●	
	Initial Phase 1 Data			●
FITUSIRAN (Hemophilia and RBD)	Phase 1 Data		●	
	Phase 1 OLE Data			●
	Start Phase 3 Studies		●	●
ALN-CC5 (Complement-Mediated Disease)	Phase 1/2 Data		●	
	Phase 2 PNH Start			●
ALN-AS1 (Hepatic Porphyrias)	Phase 1 Data			●
ALN-AAT (Alpha-1 Antitrypsin Deficiency)	Initial Phase 1 Data		●	
ALN-GO1 (Primary Hyperoxaluria)	Start Phase 1	✓		
	Initial Phase 1 Data			●
New Genetic Medicine Program	CTA Filing			●
ALN-PCSsc (Hypercholesterolemia)	Initial Phase 2 Data			●
ALN-HBV (Hepatitis B Virus Infection)	CTA Filing	✓		
	Start Phase 1		●	

Select Scientific and Clinical Meetings
Mid-2016

	Conference	Date (Location)	Expected Presentation(s)
ALN-CC5	**European Renal Association – European Dialysis and Transplant Association (ERA-EDTA)**	May 22 (Vienna)	ALN-CC5 Phase 1/2, Parts A and B (updated healthy volunteer data)
ALN-CC5	**European Hematology Association (EHA)**	June 11 (Copenhagen)	ALN-CC5 Phase 1/2, Part C (PNH patients)
Patisiran Revusiran	**International Symposium on Amyloidosis (ISA)***	July 3-8 (Uppsala)	Patisiran initial 24-month Ph 2 OLE; Revusiran initial 12-month Ph 2 OLE
Fitusiran	**World Federation of Hemophilia (WFH)**	July 27 (Orlando)	Fitusiran Phase 1, Part C (highest and fixed dose cohorts, including inhibitor patients)

*pending abstract acceptance

Q1 2016 Financial Results

Q&A Session

Thank you

Alnylam® PHARMACEUTICALS