Second Quarter 2016 Financial Results

August 4, 2016

Alnylam® PHARMACEUTICALS

Agenda

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

Q2 2016 Overview
- John Maraganore, Ph.D.
  Chief Executive Officer

Alnylam Clinical Pipeline
- Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President of R&D, Chief Medical Officer

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 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; 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 quarterly 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.

John Maraganore, Ph.D.
Chief Executive Officer

Q2 2016 Overview

Akshay Vaishnaw, M.D., Ph.D.,
Executive Vice President of R&D, Chief Medical Officer

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
- APOLLO-OLE study ongoing

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
- Phase 1 ongoing
- Phase 3 start planned for 2017

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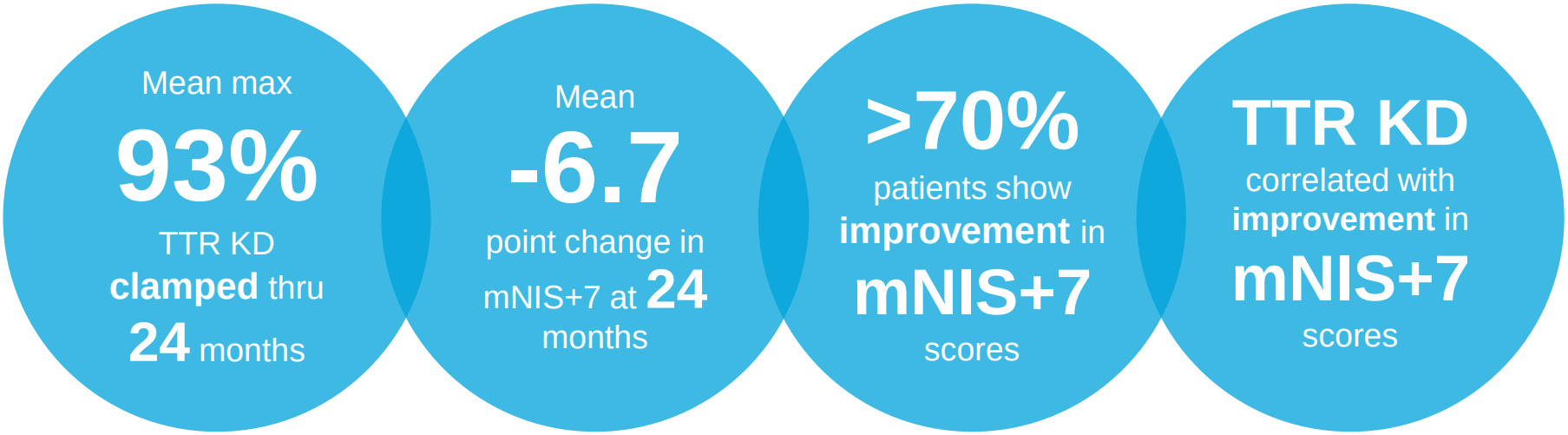
Patisiran Interim Phase 2 OLE Study Results*

Ongoing Study in hATTR-PN Patients



Evidence for Potential Halting or Improvement of Neuropathy Progression

Safety: Generally well tolerated out to 25 months

- 9 non-drug related SAEs in 6 patients
- Majority of AEs mild to moderate, including mild flushing (22.2%) and mild infusion-related reactions (18.5%)
- No significant lab findings, including platelets, and no drug-related discontinuations

PLANNED NEXT STEPS

36-month Phase 2 OLE data in **2017**

*Preliminary Phase 2 OLE results based on data in database as of May 12, 2016; Suhr, *ISA*, July 2016

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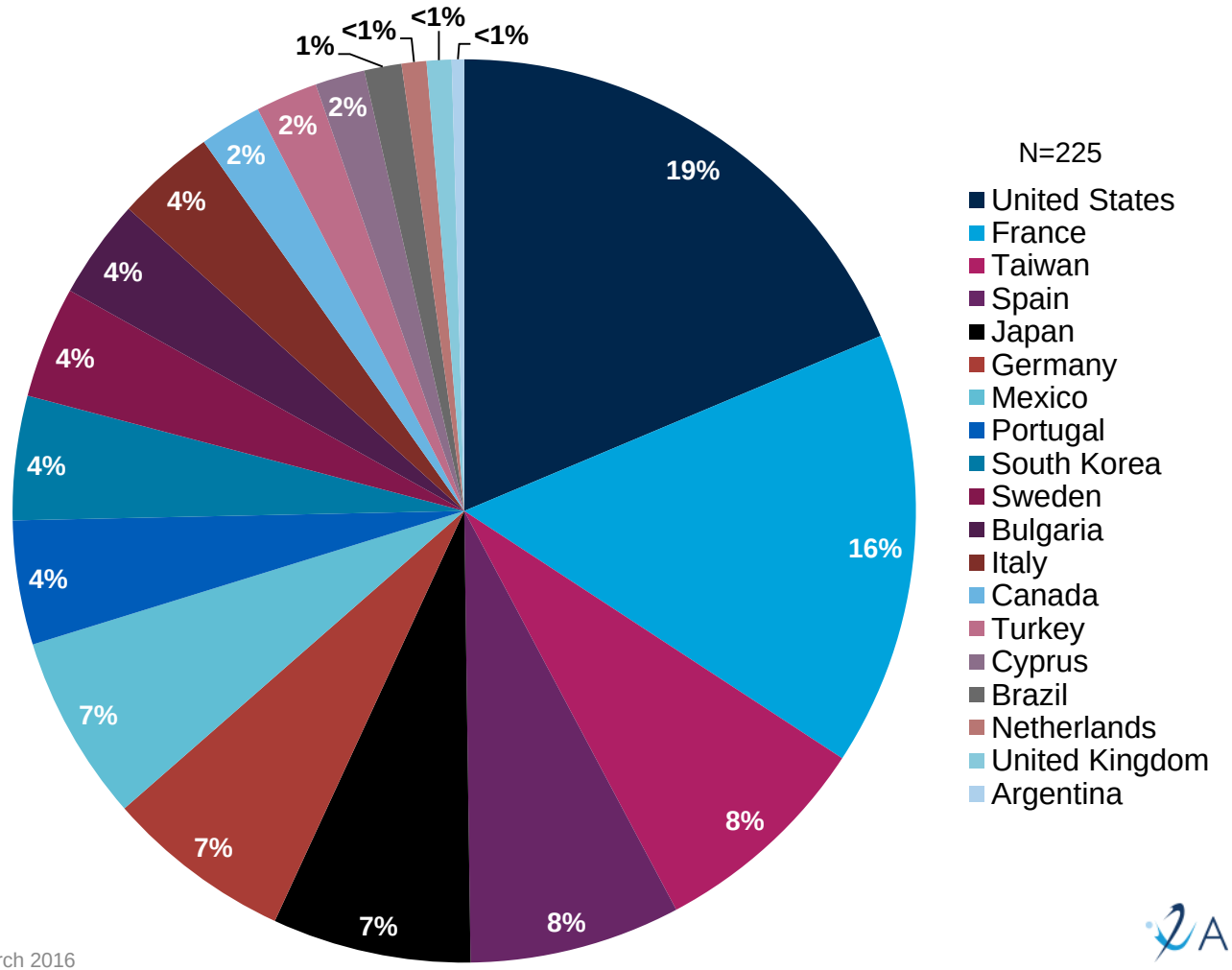
APOLLO Patisiran Phase 3 Study

Enrollment by Country

A total of 225 patients with hATTR-PN enrolled from Dec 2013 – January 2016

Patients enrolled at 44 sites in 19 countries



*Data as of 01 March 2016

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

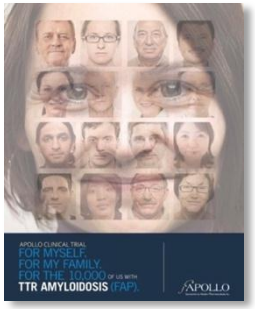
Key Secondary Endpoints
- Norfolk QOL-DN
- NIS-weakness
- mBMI
- 10-meter walk

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

Enrollment completed; mid-2017 data readout, supporting 2017 NDA and MAA if 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

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Revusiran Interim Phase 2 OLE Study Results*

Ongoing Study in ATTR Cardiomyopathy Patients

Advancing RNAi Therapeutics for the Treatment of hATTR-CM

Safety:

- Advanced study population with mean time from diagnosis to 1st dose of 35 months; published median survival of 26-43 months
- SAEs in 14 patients (56%)
  - Includes 7 deaths, all not related to drug
  - Includes 1 case of lactic acidosis deemed possibly related
- Injection site reactions (ISRs) reported in 12 patients (48%)
- 4 discontinuations (16%) due to drug related AEs
  - 1 due to lactic acidosis; 3 previously reported due to ISRs or diffuse rash; no further discontinuations due to ISRs
- Reversible LFT elevation in 1 patient resulting in dose reduction; no other notable lab abnormalities, including platelets

PLANNED NEXT STEPS

APOLLO cardiac subgroup
in **mid-2017**

ENDEAVOUR readout
in **early 2018**

*Preliminary Phase 2 OLE results as of May 26, 2016; Gillmore, *ISA*, July 2016

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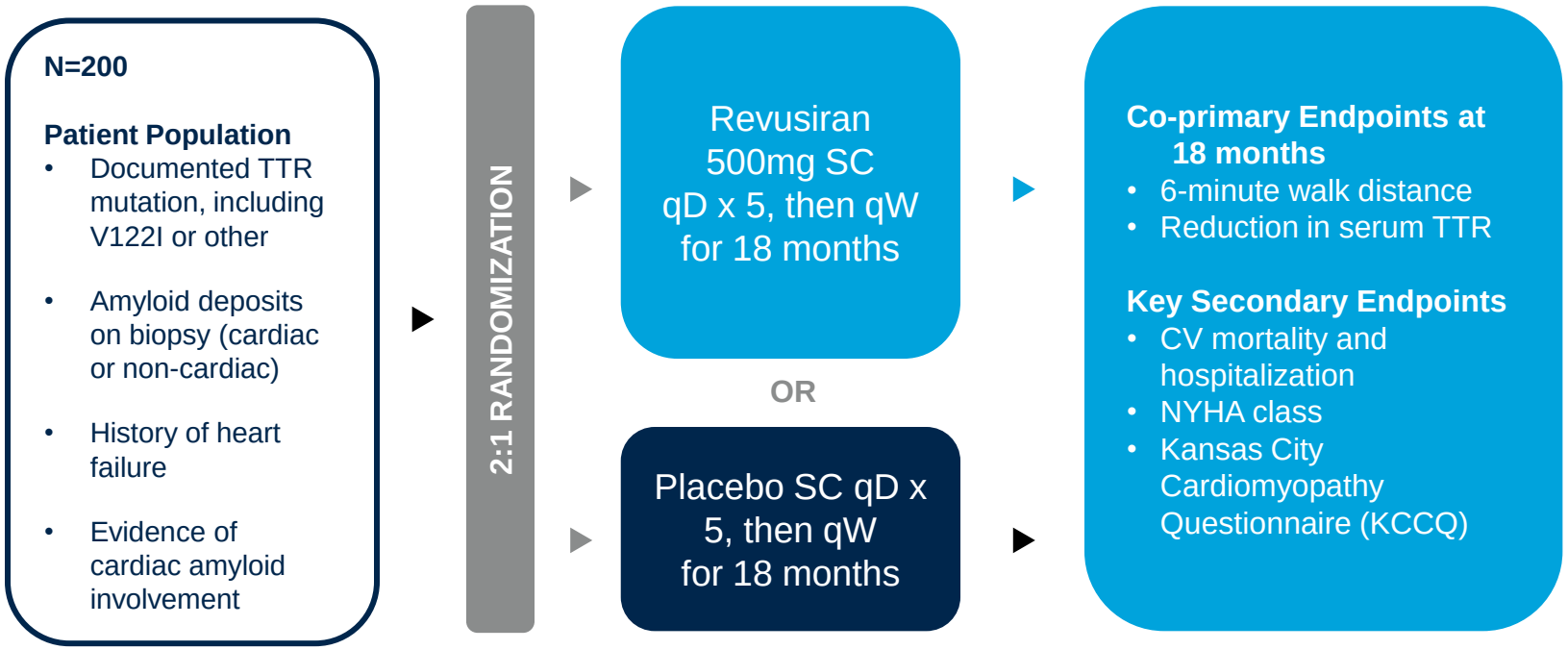
ENDEAVOUR Phase 3 Study Design



All completers eligible for revusiran treatment on Phase 3 OLE study

Expect to complete enrollment by end-summer; Report data in early 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

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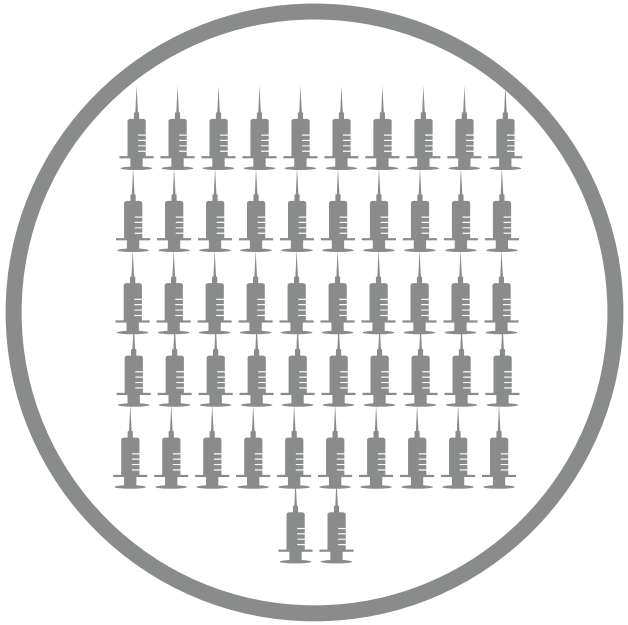
ALN-TTRsc02 Opportunity

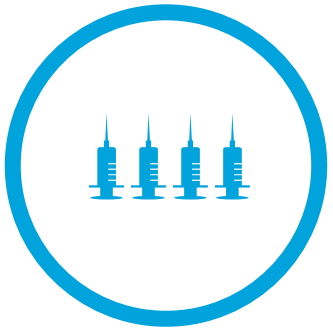
Potential for Best-in-Class Profile

Revusiran/IONIS-TTR$_{Rx}$



52 DOSES PER YEAR

ALN-TTRsc02



4 DOSES PER YEAR ANTICIPATED

PLANNED NEXT STEPS

Phase 1 started
in June 2016

Initial Data
late 2016

Phase 3 start
in 2017

Fitusiran Interim Phase 1 Study Results*

Ongoing Study in Hemophilia A & B Patients, Including Inhibitors

Up to **91%** AT lowering

Up to **mean 290%** increase in thrombin generation

Median estimated ABR of **0** in non-inhibitor patients

AT lowering, **thrombin generation increases**, and preliminary evidence of **reduced bleeding** in first inhibitor cohort

DURABILITY

Monthly SC fixed 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
  - Mild ISRs in 11 (35%) patients
- One discontinuation due to AE considered severe, possibly drug-related
  - Non-cardiac chest pain; associated transient increases in LFTs, D-dimer, CRP
  - Extensive evaluation unremarkable; VTE excluded
  - Event resolved with symptomatic management; antacids, analgesics
- No thromboembolic events; no lab evidence for pathologic clot formation

PLANNED NEXT STEPS

Additional data in **late 2016**

Start Phase 3 studies in **early 2017**

*Interim Phase 1 study results as of July 11, 2016; Pasi *et al.*, *WFH*, July 2016

ALN-CC5 Initial Phase 1/2 Study Results*

Initial Results in 6 PNH Patients

Up to **99%** **C5 KD**

LDH normalized for **1 month** with **75%** **reduction** in Ecu dose

Disease control in Ecu inadequate responder patient experiencing **breakthrough hemolysis**

Significant improvement of Ecu PK with **>3x** **increase** in Ecu trough levels

DURABILITY

Expect **quarterly** SC dose regimen

Potential opportunity to transform PNH with reduced burden of Ecu dose and frequency and to improve disease control in Ecu inadequate responder patients

Safety: Generally well tolerated

- No SAEs, no discontinuations due to AEs
- In one patient, asymptomatic, transient grade 3 elevation of LFTs observed; possibly related
- Mild, transient ISRs observed in 3 patients

PLANNED NEXT STEPS

Start PNH Phase 2
in **late 2016**

Start monotherapy Phase 2 studies in other indications
In **2017**

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*Preliminary Phase 1/2 study results based on data transferred up to June 6, 2016; Hill, *EHA*, June 2016

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

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Alpha-1 Antitrypsin (AAT) Deficiency Associated Liver Disease
ALN-AAT

DESCRIPTION

Orphan disease leading to liver cirrhosis caused by mutant AAT misfolding and aggregation in hepatocytes

PATIENT POPULATION*

~12,000
worldwide

Leading cause of **liver transplantation** in **children**

Pre-clinical results:‡

>90%
AAT Knockdown

Reduction in **fibrosis** and **liver tumors**

DRUG MECHANISM

ALN-AAT targets AAT gene to prevent aggregation of mutant protein in liver

PLANNED NEXT STEPS

Initial Phase 1/2 Data
in **mid-2016**

* Stoller *et al., GeneReviews,* 2014
‡ Sehgal, *DDW*, May 2015

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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

Pre-clinical results:‡

99%
GO mRNA silencing

98%
reduction in urinary oxalate

Phase 1/2 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*

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ALN-PCSsc* Interim Phase 1 Study Results†

Study in Volunteers with Elevated LDL-C

Potential **Bi-annual** SC Dosing Regimen with LDL-C Lowering Comparable to **Bi-monthly** mAbs**

Safety: Generally well tolerated

- No SAEs, no drug-related discontinuations; all AEs mild or moderate
- At higher drug exposures, 4 mild ISRs (8%)
- One subject with ALT ~4x ULN, attributed to concomitant statins

Phase 2 enrollment completed with

501

ASCVD patients

in **June 2016**

PLANNED NEXT STEPS‡

Initial Phase 2 data

in **late 2016**

Start Phase 3

in **2017**

* ALN-PCSsc also known as "PCSK9si"

† Preliminary Phase 1 study results as of September 24, 2015; Fitzgerald, AHA, November 2015

** Based on reported data (Zhang et al., BMC Med., 2015); no direct head-to-head studies have been performed

‡ 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

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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

Phase 1/2 Initiated

in **July 2016**

PLANNED NEXT STEPS

Initial clinical data

in **mid-2017**

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

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Michael Mason

Vice President, Finance and Treasurer

Q2 2016 Financial Results

Financial Summary and Guidance

2016 Q2 Financial Results

- Cash ~$1.28B
  - Includes $150.0 million in restricted investments
- GAAP Revenues $8.7M
- Total GAAP Operating Expenses $101.2M
  - Research and Development Expense $83.2M
  - General and Administrative Expense $18.0M
- GAAP Net Loss of $90.1M
- Shares Outstanding ~85.6M

2016 Guidance

- Year-end cash >$1.0B
  - Includes $150.0 million of restricted investments 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*

*Goals as updated in 8/16 **Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4

		2016**		
		Early	Mid	Late
PATISIRAN (hATTR-PN)	Complete APOLLO Phase 3 Accrual	✓		
	Phase 2 OLE 24 Month Data		✓	
REVUSIRAN (hATTR-CM)	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 1/2 OLE Data			●
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/Late 2016

	Conference	Date (Location)	Expected Presentation(s)
ALN-AS1	Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium	September 7 (Rome)	ALN-AS1 Phase 1, Complete data from Parts A and B (ASHE patients)
ALN-GO1	International Pediatric Nephrology Association (IPNA) Congress	September 24 (Iguaçu, Brazil)	ALN-GO1 Phase 1/2
ALN-AAT	Oligonucleotide Therapeutics Society (OTS) Annual Meeting	September 25-28 (Montreal)	ALN-AAT Phase 1/2
ALN-PCSsc	American Heart Association (AHA) Scientific Sessions*	November 12-16 (New Orleans)	ALN-PCSsc ORION-1 Phase 2
Fitusiran ALN-CC5	American Society of Hematology (ASH) Annual Meeting*	December 3-6 (San Diego)	Fitusiran Phase 1, Parts C and D (highest and fixed dose cohorts, including inhibitor patients); Initial Fitusiran Phase 1/2 OLE data; ALN-CC5 Phase 1/2 (PNH patients)
Corporate	R&D Day 2016	December 16 (New York)	

*pending abstract acceptance

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Upcoming RNAi Roundtables

Fitusiran for the treatment of Hemophilia and Rare Bleeding Disorders

Monday, August 22, 10:30 a.m. – 11:45 a.m. ET

- Akin Akinc, Ph.D., Vice President, General Manager, Fitusiran Program
- Benny Sorensen, M.D., Ph.D., Senior Director, Clinical Research
- Guest Speaker: Brian O'Mahony, Chief Executive, Irish Haemophilia Society Ltd. and person living with severe hemophilia B

ALN-CC5 for the treatment of Complement-Mediated Diseases

Wednesday, August 31, 11:00 a.m. – 12:00 p.m. ET

- Jeff Miller, Vice President, General Manager, CC5 Program
- Pushkal Garg, M.D., Senior Vice President, Clinical Development
- Guest Speaker: Anita Hill, M.D., Ph.D., MRCP, FRCPath, Consultant Haematologist for Leeds Teaching Hospitals NHS Trust, UK, and Lead for the National PNH Service in England

ALN-AS1 for the treatment of Acute Hepatic Porphyrias

Tuesday, September 13, 11:30 a.m. – 12:45 p.m. ET

- John Maraganore, Ph.D., Chief Executive Officer
- William Querbes, Ph.D., Associate Director, Research
- Guest Speaker: Ariel Lager, living with Acute Intermittent Porphyria

ALN-GO1 for the treatment of Primary Hyperoxaluria Type 1 (PH1)

Tuesday, September 27, 10:00 a.m. – 11:00 a.m. ET

- Barry Greene, President and Chief Operating Officer
- David Erbe, Ph.D., Director, Research
- Guest Speaker: Sally-Anne Hulton, M.D., FRCPCH, MRCP, FCP, MBBCh, Consultant Paediatric Nephrologist and Clinical Lead, Birmingham Children's Hospital NHS Trust
- Guest Speaker: Jennifer Lawrence, M.D. (mother of George Tidmore, a PH1 patient)

ALN-HBV for the treatment of Hepatitis B Virus (HBV) Infection

Tuesday, October 11, 9:00 a.m. – 10:00 a.m. ET

- Barry Greene, President and Chief Operating Officer
- Laura Sepp-Lorenzino, Ph.D., Vice President, Entrepreneur-in-Residence
- Guest Speaker: Heiner Wedemeyer, M.D., Managing Senior Physician and Assistant Professor in the Department of Gastroenterology, Hepatology and Endocrinology at Hannover Medical School

For more information, please visit **www.alnylam.com/roundtables**

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Q2 2016 Financial Results

Q&A Session

Thank you

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