Corporate Overview

April 2016
Please note this is an interactive PDF

Click these bubbles in order to access complete data slides

Click the safety bars in order to access additional safety data
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.
RNAi Therapeutics
New Class of Innovative Medicines

- Harness natural pathway
- Catalytic mechanism
- Silence any gene in genome
- Upstream of today’s medicines
- Clinically proven approach
Key Features of Alnylam Investigational RNAi Therapeutics

Potential Attributes for Differentiation and Value

- **UND maggable Targets**
- **Maximum Knockdown (KD) Efficacy**
  - Up to 99%
- **Pharmacodynamics (PD)**
  - NOT
- **Durability**
  - As few as 2 doses per year vs. 26 or more doses per year
- **Subcutaneous (SC) Route**
- **Room Temp**

Alnylam PHARMACEUTICALS
## Alnylam Reproducible and Modular Platform
### Strategic Framework for Innovative Medicines

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<th>1. Genetically validated, liver-expressed target gene</th>
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<td>• High unmet need disease</td>
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<td>• Opportunity for highly competitive profile</td>
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<td>• Delivery with GalNAc conjugate platform</td>
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<th>2. Biomarker for POC in Phase 1</th>
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<td>• Blood or urine based</td>
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<td>• Informative disease correlation</td>
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<td></td>
<td>• Establish dose/regimen for late-stage development</td>
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<th>3. Definable path to approval and market</th>
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<tr>
<td></td>
<td>• Clinical development plans with established endpoints</td>
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<td>• Demonstrable value for payers</td>
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Alnylam Strategic Therapeutic Areas (STArs)

Investigational pipeline focused in 3 STArs

**Genetic Medicines**
RNAi therapeutics for rare diseases

**Cardio-Metabolic Diseases**
RNAi therapeutics for dyslipidemia, NASH, type 2 diabetes, hypertension, and other major diseases

**Hepatic Infectious Diseases**
RNAi therapeutics for major liver infections beginning with hepatitis B & D
### Alnylam Development Pipeline

#### Genetic Medicines
- **Hereditary ATTR Amyloidosis**
  - DISCOVERY: Patisiran
  - DEPLOYMENT: Fitusiran
  - PHASE 2: Revusiran
- **Hemophilia and Rare Bleeding Disorders**
- **Complement-Mediated Diseases**
  - DEPLOYMENT: ALN-CC5
- **Hepatic Porphyrias**
  - DEPLOYMENT: ALN-AS1
- **Alpha-1 Antitrypsin Deficiency**
  - DEPLOYMENT: ALN-AAT
- **Primary Hyperoxaluria Type 1**
  - DEPLOYMENT: ALN-GO1
- **ATTR Amyloidosis**
  - DEPLOYMENT: ALN-TTRsc02
- **Beta-Thalassemia/Iron-Overload Disorders**
  - DEPLOYMENT: ALN-TMP
- **Hereditary Angioedema**
  - DEPLOYMENT: ALN-F12
- **Additional Genetic Medicine Programs**

#### Cardio-Metabolic Diseases
- **Hypercholesterolemia**
  - DEPLOYMENT: ALN-PCSsc
- **Hypertriglyceridemia**
  - DEPLOYMENT: ALN-AC3
- **Mixed Hyperlipidemia/Hypertriglyceridemia**
  - DEPLOYMENT: ALN-ANG
- **Hypertension/Preeclampsia**
  - DEPLOYMENT: ALN-AGT
- **Thromboprophylaxis**
  - DEPLOYMENT: ALN-F12
- **Additional Cardio-Metabolic Programs**

#### Hepatic Infectious Diseases
- **Hepatitis B Virus Infection**
  - DEPLOYMENT: ALN-HBV
- **Hepatitis D Virus Infection**
  - DEPLOYMENT: ALN-HDV
- **Chronic Liver Infection**
  - DEPLOYMENT: ALN-PDL
- **Additional Hepatic ID Programs**
Hereditary Transthyretin-Mediated Amyloidosis (hATTR)

Patisiran, Revusiran, ALN-TTRsc02
Hereditary ATTR Amyloidosis

DESCRIPTION

Orphan disease caused by mutant transthyretin (TTR) amyloid deposits in nerves, heart and other tissues

PATIENT POPULATION*

~50,000 worldwide

Significant morbidity and fatal within 2-15 years from symptom onset

hATTR Amyloidosis with polyneuropathy (hATTR-PN) 10,000
hATTR Amyloidosis with cardiomyopathy (hATTR-CM) 40,000

* Ando et al., Orphanet J Rare Dis, 2013; Ruberg et al., Circulation, 2012
# RNAi Therapeutics for hATTR Amyloidosis

## Potential for Disease Modification by Reducing Pathogenic Protein

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</table>
| 1 | Genetically validated, liver-expressed target gene | Mutant *Transthyretin (TTR)* is disease-causing protein  
   • Potential for highly competitive profile vs. TTR stabilizers |
| 2 | Biomarker for POC in Phase 1 | Serum biomarker *TTR*  
   • Causal in amyloid deposits in nerves (hATTR-PN) and heart (hATTR-CM) |
| 3 | Definable path to approval and market | Streamlined clinical development plans  
   Established Endpoints:  
   • *Neurological Impairment Score* (hATTR-PN)  
   • *6 Minute Walk Distance* (hATTR-CM) |
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
Patisiran Interim Phase 2 OLE Study Results*
Ongoing Study in hATTR-PN Patients

Mean max TTR KD clamped thru 24 months
92%

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
**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
- Placebo IV q3W

**Primary Endpoint at 18 months**
- mNIS+7

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

**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

**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**

Clinicaltrials.gov # NCT01960348
Revusiran Interim Phase 2 OLE Study Results*
Ongoing Study in hATTR-CM Patients

Mean max 87% TTR KD

Sustained and clamped TTR KD out to 6 months

Stable 6-MWD in majority of evaluable patients

No clinically meaningful changes in other cardiac measures

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
**Phase 3 Study Design**

**N=200**

**Patient Population**
- Documented TTR mutation, including V122I or other
- Amyloid deposits on biopsy (cardiac or non-cardiac)
- History of heart failure
- Evidence of cardiac amyloid involvement

**2:1 RANDOMIZATION**

**Revisiran**
- 500mg SC qD x 5, then qW for 18 months

**OR**

**Placebo SC qD x 5, then qW for 18 months**

**Co-primary Endpoints at 18 months**
- 6-minute walk distance
- Reduction in serum TTR

**Key Secondary Endpoints**
- CV mortality and hospitalization
- NYHA class
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

**All completers eligible for revusiran treatment on Phase 3 OLE study**

**Expect to report data in 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
ALN-TTRsc02 Opportunity
Potential for Best-in-Class Profile

Revusiran/IONIS-TTR$_{Rx}$

ALN-TTRsc02

52 DOSES PER YEAR

PLANNED NEXT STEPS

CTA filed in March 2016

Phase 1 start mid-2016

Initial Data late 2016

Phase 3 start in 2017

4 DOSES PER YEAR ANTICIPATED
Hemophilia and Rare Bleeding Disorders

Fitusiran
Hemophilia and Rare Bleeding Disorders

**DESCRIPTION**

Genetic deficiency resulting in inability to generate thrombin and to stop bleeding

**PATIENT POPULATION***

Hemophilia A and B

178,500 worldwide

3,500 with inhibitors

Highest need is prophylaxis for inhibitor patients and to avoid inhibitor formation in all patients

Global need due to frequent IV infusions, ability to manufacture, and cold chain

# Fitusiran for Hemophilia

Potential Game-Changing SC Therapy that Restores Hemostasis

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<tr>
<th><strong>1</strong></th>
<th>Genetically validated, liver-expressed target gene</th>
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<td></td>
<td><strong>Antithrombin (AT)</strong> is key natural anticoagulant</td>
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<td></td>
<td>• Undruggable with mAbs or small molecules (SM)</td>
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<td>Co-inheritance of AT deficiency with hemophilia associated with milder bleeding phenotype</td>
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<th><strong>2</strong></th>
<th>Biomarker for POC in Phase 1</th>
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<td>Plasma biomarkers measure components in coagulation cascade:</td>
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<tr>
<td></td>
<td>• AT</td>
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<td>• Thrombin Generation</td>
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<th><strong>3</strong></th>
<th>Definable path to approval and market</th>
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<td></td>
<td>Two separate pivotal trials in inhibitor and on-demand patients</td>
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<td>Established Endpoint: <strong>Annualized Bleeding Rate (ABR)</strong></td>
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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
Complement-Mediated Diseases

ALN-CC5
Complement-Mediated Diseases

DESCRIPTION

Numerous debilitating diseases caused by abnormal complement activity

Optimize for consistent efficacy and SC dosing option

PATIENT POPULATIONS*

- Paroxysmal nocturnal hemoglobinuria (PNH)
- Atypical hemolytic uremic syndrome (aHUS)
- Neuromyelitis optica
- Myasthenia gravis
- and many others...

>5,000 Patients with PNH & aHUS on eculizumab

* Estimated based on Alexion’s Third Quarter 2015 Financial Results
1 eculizumab, trade name Soliris®, Alexion Pharmaceuticals, Inc.
# ALN-CC5 for Complement-Mediated Diseases
## Potential New Approach for Optimized Therapy

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| **1** | **Genetically validated, liver-expressed target gene** | **Complement C5** is key component of terminal complement pathway; clinically validated in PNH & aHUS
- Potential for highly competitive profile vs. anti-C5 mAbs |
| **2** | **Biomarker for POC in Phase 1** | Serum biomarkers:
- C5
- Serum hemolytic activity
- Lactate dehydrogenase (LDH) |
| **3** | **Definable path to approval and market** | Small pivotal study in PNH patients
Established endpoints:
- LDH reduction
- Blood transfusions |
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 with or without eculizumab

Initial Evidence for Clinically Meaningful Reductions in C5 and Complement Activity

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
LDH data in PNH patients in mid- and late 2016
Start Phase 3 in 2017

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

ALN-AS1
Acute Hepatic Porphyrias

DESCRIPTION

Family of ultra-rare orphan diseases causing incapacitating and potentially fatal attacks

PATIENT POPULATION*

~5,000 Patients with sporadic attacks in U.S./EU

~1,000 Patients with recurrent attacks in U.S./EU

Symptoms include:
- Severe Abdominal Pain
- Peripheral and Autonomic Neuropathy
- Neuropsychiatric Symptoms

Predominantly female, commonly misdiagnosed

* ORPHANET; The Porphyria Consortium
### ALN-AS1 for Acute Hepatic Porphyrias
Potential Transformative Therapy to Prevent Debilitating Attacks

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| **1** | **Genetically validated, liver-expressed target gene** | **ALAS1** is upstream of genetic defect in acute hepatic porphyrias  
- Liver-specific inhibition undruggable with SM  
Up-regulation of ALAS1 results in accumulation of toxic intermediates – **ALA** and **PBG** – that drive disease |
| **2** | **Biomarker for POC in Phase 1** | Serum and urinary biomarkers:  
- **ALA**  
- **PBG** |
| **3** | **Definable path to approval and market** | Small pivotal study in recurrent attack patients  
Endpoints:  
- **Porphyria attack frequency and severity**  
- **ALA** and **PBG** levels |
ALN-AS1 Initial Phase 1 Study Results*
Ongoing Study in Asymptomatic & Symptomatic Porphyria Patients

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

DURABILITY
Monthly and possibly quarterly SC dose regimen

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

Up to 59% silencing of ALAS-1 mRNA
Up to 82% lowering of ALA
Up to 93% lowering of PBG

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

ALN-PCSsc
Hypercholesterolemia

**DESCRIPTION**

Highly prevalent disease caused by elevated levels of LDL-C that increase risk of atherosclerotic cardiovascular disease (ASCVD)

**PATIENT POPULATION**

31 million

in U.S. have LDL-C levels >240 mg/dL

About 50% of patients **discontinue** statin therapy within **one year**, and **adherence** decreases with time

Genetically defined patient subgroups: **Heterozygous FH** **Homozygous FH**

* Mozaffarian et al., Circulation, 2015
ALN-PCSsc for Hypercholesterolemia
First-in-Class PCSK9 Synthesis Inhibitor

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| **1** | Genetically validated, liver-expressed target gene | **PCSK9** protein decreases LDL-C receptor levels, resulting in elevated cholesterol in blood  
• Potential for highly competitive profile vs. anti-PCSK9 mAbs  
Loss-of-function mutations in PCSK9 associated with lower LDL-C and decreased CV risk |
| **2** | Biomarker for POC in Phase 1 | Serum biomarkers for regulation of cholesterol levels:  
• **PCSK9**  
• **LDL-C** |
| **3** | Definable path to approval and market | Pivotal trial in broad population of ASCVD patients; focused FH studies  
Established Endpoint: **LDL-C** |
ALN-PCSsc Interim Phase 1 Study Results*
Study in Volunteers with Elevated LDL-C

**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

**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

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

- Up to 94% PCSK9 KD
- Up to 64% mean maximum LDL-C lowering
- At 6 months 47% LSM reduction in LDL-C after 1 dose

**PLANNED NEXT STEPS‡**
- Initial Phase 2 data in late 2016
- Start Phase 3 in 2017
Other Programs to Watch in 2016
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

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

PLANNED NEXT STEPS
Initial Phase 1 Data in mid-2016

Pre-clinical results:‡
>90% AAT Knockdown
Reduction in fibrosis and liver tumors

Leading cause of liver transplantation in children

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

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

99% GO mRNA silencing

98% reduction in urinary oxalate

Pre-clinical results‡:

Phase 1 initiated in March 2016

PLANNED NEXT STEPS
Initial clinical data in late 2016

‡ Erbe, ESPN, September 2015
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
Guidance and Goals
3 STArts
3 Marketed Products
10 Clinical Programs
4 Late Stage Programs
Potential Multi-Year Pipeline Progression

- **Patisiran** (Hereditary ATTR Amyloidosis with Polyneuropathy)
  - Phase 2 OLE
  - APOLLO Phase 3
  - Phase 3 OLE

- **Revasiran** (Hereditary ATTR Amyloidosis with Cardiomyopathy)
  - Phase 2 OLE
  - ENDEAVOUR Phase 3

- **ALN-TTRsc02** (ATTR Amyloidosis)
  - Phase 1
  - Phase 3

- **Fitusiran**
  - ALN-AT3 (Hemophilia and RBDs)
    - Phase 1
    - Phase 1 OLE
    - Phase 3

- **ALN-CC5** (Complement Disease)
  - Phase 1/2
  - Phase 1/2 OLE
  - Phase 3 PNH
  - Phase 3 Other

- **ALN-AS1** (Hepatic Porphyrías)
  - Phase 1
  - Phase 1 OLE
  - Phase 3

- **ALN-AAT** (Alpha-1 Antitrypsin Deficiency)
  - Phase 1
  - Phase 2
  - Phase 3

- **ALN-GO1** (Primary Hyperoxaluria)
  - Phase 1
  - Phase 2/3

- **ALN-PCSsc** (Hypercholesterolemia)
  - Phase 2
  - Phase 3

- **ALN-HBV** (Hepatitis B Virus Infection)
  - Phase 1
  - Phase 2

**Additional Programs**
- Research
- Additional Phase 1 and 2 Studies
# Potential Multi-Year Pipeline Progression

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<thead>
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<th>Product</th>
<th>Disease</th>
<th>2016</th>
<th>2017</th>
<th>Subsequent 1-2 Years</th>
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<td>Patisran</td>
<td>Hereditary ATTR Amyloidosis with Polyneuropathy</td>
<td>Phase 2 OLE</td>
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<td>APOLLO Phase 3</td>
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<td>Phase 3 OLE</td>
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<td>Revasiran</td>
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<td>Phase 3</td>
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<td>Fitusiran</td>
<td>ALN-AT3 (Hemophilia and RBDs)</td>
<td>Phase 1</td>
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<td>Phase 3</td>
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<td>ALN-CC5</td>
<td>Complement Disease</td>
<td>Phase 1/2</td>
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<td>Phase 1/2 OLE</td>
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<td>Phase 3 PNH</td>
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<td>Phase 2</td>
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<td>ALN-HBV</td>
<td>Hepatitis B Virus Infection</td>
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<td>Additional Phase 1 and 2 Studies</td>
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</table>

>10 Clinical readouts in 2016
Potential Multi-Year Pipeline Progression

Programs in Phase 3 in 2017

- Patisiran (Hereditary ATTR Amyloidosis with Polyneuropathy)
  - Phase 2 OLE
  - APOLLO Phase 3
  - Phase 3 OLE

- Revusiran (Hereditary ATTR Amyloidosis with Cardiomyopathy)
  - Phase 2 OLE
  - ENDEAVOUR Phase 3

- ALN-TTRsc02 (ATTR Amyloidosis)
  - Phase 1
  - Phase 3

- Fitusiran (ALN-AT3, Hemophilia and RBDs)
  - Phase 1
  - Phase 1 OLE
  - Phase 3

- ALN-CC5 (Complement Disease)
  - Phase 1/2
  - Phase 1/2 OLE
  - Phase 3 PNH
  - Phase 3 Other

- ALN-AS1 (Hepatic Porphyrias)
  - Phase 1
  - Phase 1 OLE
  - Phase 3

- ALN-AAT (Alpha-1 Antitrypsin Deficiency)
  - Phase 1
  - Phase 2
  - Phase 3

- ALN-GO1 (Primary Hyperoxaluria)
  - Phase 1
  - Phase 2/3

- ALN-PCSsc (Hypercholesterolemia)
  - Phase 2
  - Phase 3

- ALN-HBV (Treibitis B Virus Infection)
  - Phase 1
  - Phase 2

- Additional Programs
  - Research
  - Additional Phase 1 and 2 Studies

>5 Programs in Phase 3 in 2017
## Potential Multi-Year Pipeline Progression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Phase 2 OLE</th>
<th>Phase 3 OLE</th>
<th>2016 Clinical Data Expected</th>
<th>2017 Clinical Data Expected</th>
<th>Subsequent 1-2 Years</th>
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<tbody>
<tr>
<td><strong>Patisiran</strong></td>
<td>(Hereditary ATTR Amyloidosis with Polyneuropathy)</td>
<td>APOLLO Phase 3</td>
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<td><strong>Revisiran</strong></td>
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<tr>
<td><strong>ALN-TTRsc02</strong></td>
<td>(ATTR Amyloidosis)</td>
<td>Phase 1</td>
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<tr>
<td><strong>Fitusiran</strong></td>
<td>ALN-AT3 (Hemophilia and RBDs)</td>
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<tr>
<td><strong>ALN-CC5</strong></td>
<td>(Complement Disease)</td>
<td>Phase 1/2</td>
<td>Phase 3 PNH</td>
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<td><strong>ALN-AS1</strong></td>
<td>(Hepatic Porphyrias)</td>
<td>Phase 1</td>
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<tr>
<td><strong>ALN-AAT</strong></td>
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<tr>
<td><strong>ALN-GO1</strong></td>
<td>(Primary Hyperoxaturia)</td>
<td>Phase 1</td>
<td>Phase 2/3</td>
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<tr>
<td><strong>ALN-PCSsc</strong></td>
<td>(Hypercholesterolemia)</td>
<td>Phase 2</td>
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<tr>
<td><strong>ALN-HBV</strong></td>
<td>(Hepatitis B Virus Infection)</td>
<td>Phase 1</td>
<td>Phase 2</td>
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<td><strong>Additional Programs</strong></td>
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</tbody>
</table>

- **1st Phase 3 data readout and, if positive, NDA in 2017**
# Alnylam 2016 Pipeline Goals

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

<table>
<thead>
<tr>
<th>Program</th>
<th>Phase 1</th>
<th>Phase 2 OLE 12 Month Data</th>
<th>Phase 2 OLE 24 Month Data</th>
<th>Complete APOLLO Phase 3 Accrual</th>
<th>ENDEAVOUR Phase 3 Accrual</th>
<th>Phase 1 Data</th>
<th>Phase 1 OLE Data</th>
<th>Start Phase 3 Studies</th>
<th>CTA Filing</th>
<th>Initial Phase 1 Data</th>
<th>Start Phase 1</th>
<th>Initial Phase 1 Data</th>
<th>CTA Filing</th>
<th>Initial Phase 2 Data</th>
<th>Start Phase 1</th>
<th>CTA Filing</th>
<th>Initial Phase 1 Data</th>
<th>Start Phase 1</th>
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<td>REVSUSIRAN (Hereditary ATTR Amyloidosis with Cardiomyopathy)</td>
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<td>ALN-TTRsc02 (ATTR Amyloidosis)</td>
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<td>FITUSIRAN (Hemophilia and RBD)</td>
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</table>
Financial Summary and Guidance

2015 Q4 Financial Results

• Cash ~$1.28B
• GAAP Revenues $7.6M
• Total GAAP Operating Expenses $100.0M
  ◦ Research and Development Expense $82.8M
  ◦ General and Administrative Expense $17.2M
• GAAP Net Loss of $90.7M
• Shares Outstanding ~85.1M

2016 Guidance

• Year-end cash >$850M
Thank You
Backup Slides
Patisiran Phase 2 OLE Preliminary Study Results*

Summary of Safety

- 5 patients (18.5%) with 8 reports of serious adverse events (SAEs); not related to study drug
  - One discontinuation for gastroesophageal cancer at ~20 months; patient subsequently died Aug 2015
  - One patient with 3 reports (distal femur fracture/proximal tibia fracture/osteonecrosis/ligament rupture, dehydration/acute prerenal failure/urinary tract infection and thermal burn); one patient with 2 reports (ankle fracture/foot fracture/osteonecrosis and ankle arthrodesis); one patient with venous thrombosis of the lower limb; one patient with foot abscess and osteomyelitis

- Majority of AEs were mild or moderate
  - 3 patients (11.1%) had severe events not related to study drug
  - Most common related AEs reported in > 3 patients were flushing (6 patients [22.2%]) and infusion related reaction (5 patients [18.5%]), all of which were mild

- No clinically significant changes in liver function tests, renal function, or hematologic parameters, including platelets

NOTE: Post data cut-off, a 79 year old patient who completed 24 months of treatment had a SAE of myocardial infarction (not related to study drug) resulting in death (March 2016)

Common Adverse Events (AEs) in ≥10% of patients

<table>
<thead>
<tr>
<th>AE by Preferred Term</th>
<th>Patisiran (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Wound</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>3 (11.1%)</td>
</tr>
</tbody>
</table>
Patisiran Phase 2 OLE Preliminary Study Results*
Serum TTR Knockdown

- Mean serum pre-dose TTR knockdown of approximately 80%
- Mean maximal serum post-dose TTR knockdown of 92%
- Maximal individual patient post-dose knockdown of 97%
- Similar TTR knockdown in patients on patisiran alone or on patisiran + TTR tetramer stabilizers

*Data as of February 23, 2016
Partial imputation was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit).

### Change in mNIS+7 Over 18 Months

<table>
<thead>
<tr>
<th>mNIS+7 component</th>
<th>Mean (SEM)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong>*</td>
<td>-0.8 (2.7)</td>
<td>-3.1 (-26.9, 35.8)</td>
</tr>
<tr>
<td>NIS-weakness</td>
<td>0.7 (1.2)</td>
<td>0 (-8.0, 18.3)</td>
</tr>
<tr>
<td>NIS-reflexes</td>
<td>0.7 (0.7)</td>
<td>0 (-6.0, 10.0)</td>
</tr>
<tr>
<td>QST</td>
<td>-2.2 (2.1)</td>
<td>-3 (-24.0, 21.0)</td>
</tr>
<tr>
<td>NCS Σ5</td>
<td>0.1 (0.2)</td>
<td>0 (-1.5, 2.5)</td>
</tr>
<tr>
<td>Postural BP</td>
<td>0 (0.1)</td>
<td>0 (-1.5, 1.0)</td>
</tr>
</tbody>
</table>

*Data as of February 23, 2016

*Partial imputation was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit)
Patisiran Phase 2 OLE Preliminary Study Results*
Correlation of TTR Knockdown with ΔmNIS+7

Note: three patients had missing D17 TTR: one was replaced by D7 and two replaced by D84.
† Percent (%) TTR knockdown from baseline at Day 17 post-first dose of patisiran

*Data as of February 23, 2016
Patisiran Phase 2 OLE Preliminary Study Results*
Sweat Gland Nerve Fiber Density (SGNFD): Lower Limb

- Blinded analysis of tandem skin punch biopsies performed at central lab
- Statistically significant increase in distal thigh SGNFD at both 12 and 18 months
- Increase in distal leg SGNFD at both 12 and 18 months, although not significant
- In a separate study in hATTR-PN patients with the highly pathogenic A97S mutation, SGNFD correlated to autonomic system involvement and disability burden

** 2-sided p values from paired t-test comparing post-baseline vs baseline
†Chao C et al., Ann Neurol. 78:272-83 (2015)
*Data as of February 23, 2016
Revusiran Phase 2 OLE Preliminary Results*  
Summary of Safety

<table>
<thead>
<tr>
<th>Most common adverse events ≥10%†</th>
<th>All subjects (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with an adverse event, n (%)</td>
<td>22 (88%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Contusion</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3 (12%)</td>
</tr>
</tbody>
</table>

- 8 (32%) patients with serious adverse events (SAEs) – all unrelated
  - 1 death due to infiltrative cardiomyopathy (not related)
- Majority of patients had AEs that were mild or moderate in severity
  - 5 (20%) patients with severe AEs
- Injection site reactions‡ were reported in 11 (44%) patients
  - Most common symptoms were erythema, pruritus, pain or swelling at the injection site
  - Majority of symptoms were mild in severity
  - ISRs were the most common reported related AEs
- 3 patients discontinued study drug due to recurrent localized reactions at the injection site or diffuse rash
- 2 dose reductions to 250 mg weekly
  - 1 patient for recurrent injection site reactions and
  - 1 patient for LFT elevation which resolved with continued dosing
- No other notable changes in liver function tests, renal function or hematologic parameters

---

†By preferred term in MedDRA
‡By High Level Term in MedDRA
*Data transfer 12Oct2015; Gilmore, EC-ATTR, November 2015
Revusiran Phase 2 OLE Preliminary Study Results*
Durable TTR Knockdown (KD) through 6 Months

Results as of October 13, 2015; Gilmore, EC-ATTR, November 2015
Revusiran Phase 2 OLE Preliminary Results
6-MWD in Individual Patients

<table>
<thead>
<tr>
<th>hATTR-CM</th>
<th>No Imputation</th>
<th>With Imputation</th>
</tr>
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<tbody>
<tr>
<td>Baseline N</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Mean (±SEM)</td>
<td>476 (36)</td>
<td>408 (54)</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>488 (316,617)</td>
<td>438 (73,617)</td>
</tr>
<tr>
<td>Δ 6 Months [meters] N</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Mean (±SEM)</td>
<td>-20 (14)</td>
<td>-43 (21)</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>-3 (-81, 27)</td>
<td>-29 (-199, 27)</td>
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</table>

<table>
<thead>
<tr>
<th>wtATTR</th>
<th>No Imputation</th>
<th>With Imputation</th>
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</thead>
<tbody>
<tr>
<td>Baseline N</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Mean (±SEM)</td>
<td>407 (23)</td>
<td>394 (24)</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>427 (308, 464)</td>
<td>423 (305, 464)</td>
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<tr>
<td>Δ 6 Months [meters] N</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Mean (±SEM)</td>
<td>-24 (20)</td>
<td>-59 (39)</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>-6 (-122, 35)</td>
<td>-9 (-305, 35)</td>
</tr>
</tbody>
</table>

*2 hATTR-CM(■) and 1 wtATTR(□) patients imputed 6-MWD (6-Minute Walk Distance) as 0 meters at 6 months (Patients were unable to perform test at planned visit)
NH: Natural History
*Data transfer 12Oct2015 ; Gilmore, EC-ATTR, November 2015
# Revusiran Phase 2 OLE Preliminary Results*

## Clinical Measurements

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N**</th>
<th>Baseline Mean (SEM)</th>
<th>6 Month Mean (SEM)</th>
<th>Changes From Baseline Mean (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mBMI (kg/m(^2) × albumin [g/L])</td>
<td>17</td>
<td>1162 (52.3)</td>
<td>1065 (56.1)</td>
<td>-97 (15.6)</td>
</tr>
<tr>
<td>KCCQ Overall Summary Score</td>
<td>17</td>
<td>68.8 (4.7)</td>
<td>61.2 (5.7)</td>
<td>-7.5 (3.5)</td>
</tr>
<tr>
<td>EQ-5D (max impairment=0)</td>
<td>17</td>
<td>0.80 (0.03)</td>
<td>0.75 (0.04)</td>
<td>-0.05 (0.03)</td>
</tr>
</tbody>
</table>

**Cardiac Biomarkers**

- NT-proBNP (ng/L)
  - N**: 17
  - Baseline: 3454 (1173)
  - 6 Month: 3853 (979)
  - Δ: 399 (321)
- Troponin I (ng/mL)
  - N**: 17
  - Baseline: 0.12 (0.02)
  - 6 Month: 0.14 (0.03)
  - Δ: 0.02 (0.02)

**Echocardiogram**

- IVS Thickness (cm)
  - N**: 15
  - Baseline: 2.00 (0.10)
  - 6 Month: 2.03 (0.10)
  - Δ: 0.03 (0.03)
- LVEF (%)
  - N**: 15
  - Baseline: 46.9 (3.3)
  - 6 Month: 47.9 (3.9)
  - Δ: 1.1 (2.3)
- Longitudinal Strain (%)
  - N**: 15
  - Baseline: -12.0 (1.1)
  - 6 Month: -12.7 (0.9)
  - Δ: -0.8 (0.5)

**Cardiac MRI**

- LV Mass (g)
  - N**: 11
  - Baseline: 215.1 (24.7)
  - 6 Month: 231.9 (21.4)
  - Δ: 16.8 (14.4)
- Stroke Volume (mL)
  - N**: 11
  - Baseline: 71.9 (6.6)
  - 6 Month: 76.9 (3.9)
  - Δ: 4.9 (5.0)
- Global ECV
  - N**: 10
  - Baseline: 0.53 (0.02)
  - 6 Month: 0.51 (0.03)
  - Δ: -0.01 (0.02)

---

KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ-5D score uses US references; mBMI: Modified Body Mass Index; IVS: Interventricular Septum; ECV: Extracellular Volume Fraction

*Includes results for pooled hATTR-CM and wtATTR patients with available data at baseline and 6 months

*Data transfer 12Oct2015; Gilmore, EC-ATTR, November 2015
Superior TTR Knockdown with ALN-TTRsc02
ALN-TTRsc02 Compared to Revusiran in NHP**

**Data on graph does not represent a side by side study. The two NHP studies were performed independently.
Interim Fitusiran Phase 1 Study Results*
Safety/Tolerability, Parts B & C†

• No SAEs related to study drug and no discontinuations
  ◦ One subject was hospitalized due to re-activation of hepatitis C, not drug related

• AEs reported
  ◦ Total of 35 AEs occurred in 14 patients
    – 33 single AEs + 2 AE episodes of arthritis
    – 34 Mild/Moderate, 1 Severe‡
  ◦ 3 drug related AEs were observed – all mild:
    – Injection site reactions:
      » One patient (45 mcg/kg) experienced mild transient pain
      » One patient (1800 mcg/kg) experienced mild transient erythema & pain
    – Other:
      » Headache, transient
  ◦ No thromboembolic events or clinically significant D-dimer increases
  ◦ No drug related clinically significant changes in physical exams, vital signs, ECG or laboratory parameter (LFTs, CBC, coagulation)
  ◦ Bleed events successfully managed with standard replacement factor administration

• No instances of anti-drug antibody (ADA) formation

*Data as of 12 November 2015; Pasi et al., ASH, December 2015
†Adverse event grouping based on MedDRA-coded terms, excluding bleed events
‡Hypertriglyceridemia
Interim Fitusiran Phase 1 Study Results*
AT Lowering, Part C

AT lowering after monthly dosing in patients with hemophilia A and B

**Dose Group**
- 225 mcg/kg (N=3)
- 450 mcg/kg (N=3)
- 900 mcg/kg (N=3)
- 1800 mcg/kg (N=3)

**Analysis Quartiles**

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Mean Max AT Lowering ± SEM</th>
<th>Max AT Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>225 mcg/kg (N=3)</td>
<td>70 ± 9%</td>
<td>80%</td>
</tr>
<tr>
<td>450 mcg/kg (N=3)</td>
<td>77 ± 5%</td>
<td>85%</td>
</tr>
<tr>
<td>900 mcg/kg (N=3)</td>
<td>78 ± 7%</td>
<td>88%</td>
</tr>
<tr>
<td>1800 mcg/kg (N=3)</td>
<td>79 ± 3%</td>
<td>84%</td>
</tr>
</tbody>
</table>

*Data as of 12 November 2015; Pasi et al., ASH, December 2015
Interim Fitusiran Phase 1 Study Results*
Thrombin Generation, Part B & C

Post hoc analysis of thrombin generation by AT lowering quartiles

<table>
<thead>
<tr>
<th>AT Lowering</th>
<th>Peak Thrombin Generation, nM (Mean ± SD)</th>
<th>% Increase in Peak Thrombin Generation (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>18 ± 9</td>
<td>20 ± 72%</td>
</tr>
<tr>
<td>25-50%</td>
<td>26 ± 12</td>
<td>48 ± 61%</td>
</tr>
<tr>
<td>50-75%</td>
<td>47 ± 29</td>
<td>218 ± 272%</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>62 ± 27**</td>
<td>285 ± 165%**</td>
</tr>
</tbody>
</table>

**p < 0.001, compared with AT lowering less than 25%

*Data as of 12 November 2015; reruns conducted on samples with analytical errors
Pasi et al., ASH, December 2015
Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events, Part C†

Prospectively collected bleed events during Onset (Day 0-28) and Observation periods (Day 29 to last available, to maximum of Day 112)

- Available Median Part C (Cohorts 1-3) Observation Period ABR = 4.3 (85% reduction relative to median Historical On-Demand ABR)
- Median Cohort 2 & 3 Observation Period ABR = 2.2 (92% reduction relative to median Historical On-Demand ABR)

*Data as of 12 November 2015; Pasi et al., ASH, December 2015
†Observation Period data for Cohort 4 (1800 mcg/kg) not yet available
#Historical On-Demand ABR value not available; excluded from summary median ABR calculation
Initial ALN-CC5 Phase 1 Study Results*
Safety and Tolerability – SAD & MAD

No SAEs and no discontinuations due to AEs

Total of 29 AEs reported in SAD phase
- All reported AEs mild or moderate in severity
- Most common (≥10%) AEs: headache, influenza-like illness, nasopharyngitis, nausea, injection site pain, seasonal allergy
- 3 AEs possibly related to treatment
  - nasopharyngitis, injection site pain, injection site rash‡
- ISRs seen in 2 subjects - all mild and transient

Total of 30 AEs reported in MAD phase
- All reported AEs mild or moderate in severity
- Most common (≥10%) AEs: headache, nasopharyngitis, vulvovaginal candidiasis
- 12 AEs possibly related to treatment
  - headache, bruise, cold symptoms, injection site edema, vaginal thrush, redness at injection site, itching at injection site, mouth ulcer
- ISR seen in 4 subjects – all mild, and transient

No clinically significant changes in vital signs, EKG, physical exams or clinical laboratories

Safety results currently blinded to treatment with ALN-CC5 or Placebo

*Data as of 10/19/2015; Sorensen, ASH, December 2015
‡ Currently coded in database as rash
ALN-CC5 Phase 1/2: Part A (SAD)*
Pharmacodynamics and Clinical Activity: Serum C5

Serum C5 knockdown following single dose of ALN-CC5

- Maximum C5 knockdown relative to baseline up to 99%
- Mean maximum C5 knockdown of 98 ± 0.9% (mean ± SEM)
- Mean C5 knockdown of 96 ± 1.0% (mean ± SEM) at Day 98 (900 mg)
Serum C5 knockdown following 5 weekly doses of ALN-CC5

- Maximum C5 knockdown relative to baseline up to 99%
- Mean maximum C5 knockdown of \(98 \pm 0.5\%\) (mean ± SEM)
- Mean C5 knockdown of \(98 \pm 0.3\%\) (mean ± SEM) at Day 112 (5 x qw, 200 mg)

![Graph showing serum C5 knockdown over time for different cohorts and placebo.](image-url)

* Data as of 10/19/2015; Sorensen, ASH, December 2015
Free and Residual C5

Eculizumab and free C5 levels (μg/mL)¹
- Eculizumab concentration-effect relationship for reduction in free C5 in aHUS patients
- Free C5 measured using validated electrochemiluminescence immunoassay
- Maximum % inhibition free C5 of 93.5%

ALN-CC5 and residual C5 levels (μg/mL)*
- Serum C5 levels after multiple doses of ALN-CC5 in healthy human volunteers
- Residual C5 levels measured using validated LCMS assay
- Maximum % inhibition residual C5 of 99%

*Data as of 10/19/2015; Sorensen, ASH, December 2015
¹There are no head to head studies comparing eculizumab and ALN-CC5
¹ASCPT Annual Meeting, Atlanta, GA; March 18-22, 2014; Abstract # 387

Residual C5 levels achieved with ALN-CC5 healthy volunteers comparable with free C5 levels in aHUS patients on eculizumab†
ALN-CC5 Phase 1/2 Part B – MAD*
Pharmacodynamics and Clinical Activity: Hemolysis Inhibition

Inhibition of sheep erythrocyte hemolysis
- 5 weekly doses of ALN-CC5
- Maximum serum hemolysis inhibition relative to baseline up to 98%
- Mean maximum serum hemolysis inhibition of 84 ± 7.6% (mean ± SEM)

* Data as of 10/5/2015; Sorensen, ASH, December 2015
ALN-AS1 Phase 1 Study Initial Results*
Safety and Tolerability

ALN-AS1 generally well tolerated
- No SAEs related to study drug and no discontinuations
  - One patient (0.10 mg/kg dose) required hospitalization for abdominal pain considered unlikely related to ALN-AS1
- Other AEs reported; all mild-moderate in severity
  - 9 AEs occurred in 4 placebo patients and 19 AEs occurred in 12 ALN-AS1-treated patients
  - No dose-related trend observed
  - No event occurred in more than one treated subject
  - One patient (1 mg/kg dose) experienced a mild, transient injection site reaction (erythema)
- No clinically significant laboratory abnormalities related to study drug
  - One patient (0.35 mg/kg dose) had increased AST, ALT, CPK and myoglobin
    - Attributed to starting intensive weight lifting program that resolved with cessation of exercise

*Data in database as of 02 September 2015; Sardh et al., ICPP, December 2015
ALN-AS1 Initial SAD Phase 1/2 Results*
ALAS1 mRNA Silencing and Lowering of ALA and PBG

Potent, dose-dependent, and durable ALAS1 mRNA silencing after single dose
- ALAS1 mRNA elevated ~3-fold in asymptomatic “high excreter” (ASHE) patients with AIP
- Up to 59% silencing and up to 44 ± 8% mean (SEM) maximal silencing; p<0.01 vs. Placebo

Lowering of ALA and PBG, toxic heme synthesis intermediates that mediate attacks
- Potent, dose-dependent, and durable effects
- Up to 82% and 93% lowering of ALA and PBG, respectively; Up to mean maximal reduction of 77 ± 7% for ALA (p=0.03) and 73 ± 6% for PBG (p=0.06)

*Data in database as of 02 September 2015; Sardh et al., ICPP, December 2015
ALN-AAT in Non Human Primates (NHP) Pre-Clinical Results

- 1mg/kg q1w x 12 and 3mg/kg q1m show similar knock-down
- AAT levels maintained for ~50 days post last dose

Relative AAT Levels (Prebleed = 1)

Days Post First Dose

- Last dose administered
Z-AAT Knockdown Improves Liver Histology and Decreases Tumor Burden in Tg-PiZ Mice

PBS Treated Animal

AAT-siRNA Treated Animal

Proliferating Cells

Tumor Incidence

Number of Tumors

Tumor Size

Sehgal, DDW, May 2015
ALN-GO1 in Non-human Primates
Potent mRNA Silencing, Expected Increases in Serum Glycolate

<table>
<thead>
<tr>
<th>Group #</th>
<th>Dose Level (mg/kg)</th>
<th>Dose Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Veh</td>
<td>qMx6</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>qWx8</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>qWx8</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>qMx6</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>qWx4 → qMx5</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>qMx5</td>
</tr>
</tbody>
</table>

Up to 99% silencing of HAO1 mRNA in non-human primates
ALN-GO1 Substantially Lowered Urinary Oxalate in Rat PH1 Model

Oxalate decreased up to 98% following weekly dosing

Note: >95% HAO1 mRNA silencing at all doses
Initial ALN-PCSsc Phase 1 Study Results*

Safety Summary

ALN-PCSsc generally well tolerated following single and multiple subcutaneous doses:

- No SAE’s and no discontinuations due to AE’s
- Most common AE’s (>10% or more of ALN-PCSsc subjects)
  - Single dose (N=18): cough, musculoskeletal pain, nasopharyngitis
  - Multiple dose (N=33): headache, back pain, diarrhea, nausea
- All AE’s mild or moderate in severity
- AE profile generally similar with or without concomitant statins
- At higher drug exposures, 4 subjects experienced mild, localized, injection site reactions
- One subject developed clinically significant changes in LFT’s
  - ALT ~4x ULN without rise in bilirubin
  - Attributed to concomitant statin therapy; resolved on D/C of statin, recurred on statin re-challenge

* Data reported are from database transfer Sept.24th 2015; Fitzgerald, AHA, November 2015
Initial ALN-PCSsc Phase 1 Study Results*
MD PCSK9 Knockdown Relative to Baseline

Max PCSK9 knockdown of 94.4% with mean max of 88.5 ± 1.6%

*Data reported are from database transfer Sept. 24th 2015; Fitzgerald, AHA, November 2015
Initial ALN-PCSsc Phase 1 Study Results*
MD LDL-C Lowering Relative to Baseline

Mean (+/- SEM) LDL-C Reduction Relative to Baseline

max LDL-C reduction of 83.0% with mean max of 64.4 ± 5.4%

*S* = On a stable dose of statins
Two MD subjects excluded:
One placebo subject elected to discontinue;
One subject in 300 mg statin group was incarcerated on Day 14

*Data reported are from database transfer Sept. 24th 2015; Fitzgerald, AHA, November 2015
## Initial ALN-PCSsc Phase 1 Study Results*

Least Square Mean %Change in LDL-C by Beta Quantification

<table>
<thead>
<tr>
<th>SAD</th>
<th>LSM % change at group nadir (N)</th>
<th>LSM % change day 84 (N)</th>
<th>LSM % change day 140 (N)</th>
<th>LSM % change day 180 (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300mg</td>
<td>-50.0 (3) **</td>
<td>-50.0 (3) **</td>
<td>-43.1 (3)</td>
<td>-47.0 (3)</td>
</tr>
<tr>
<td>500mg</td>
<td>-59.0 (3) **</td>
<td>-50.5 (3) **</td>
<td>-38.8 (2)</td>
<td>-36.3 (2)</td>
</tr>
<tr>
<td>800mg</td>
<td>-52.8 (6) **</td>
<td>-43.3 (5) **</td>
<td>-49.3 (4)</td>
<td>ongoing</td>
</tr>
</tbody>
</table>

Max LDL-C day 180; 53%

<table>
<thead>
<tr>
<th>MD</th>
<th>LSM % change at group nadir (N)</th>
<th>LSM % change day 84 (N)</th>
<th>LSM % change day 140 (N)</th>
<th>LSM % Change day 208 (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300mg</td>
<td>-59.5 (6) ***</td>
<td>-59.5 (6) ***</td>
<td>-50.8 (6)</td>
<td>-44.4 (5)</td>
</tr>
<tr>
<td>300mg S</td>
<td>-53.4 (3) *</td>
<td>-46.6 (3) *</td>
<td>-39.2 (3)</td>
<td>ongoing</td>
</tr>
<tr>
<td>500mg</td>
<td>-53.5 (6) ***</td>
<td>-51.9 (6) ***</td>
<td>-53.8 (6)</td>
<td>ongoing</td>
</tr>
<tr>
<td>500mg S</td>
<td>-59.9 (4) ***</td>
<td>-53.2 (5) ***</td>
<td>-53.0 (3)</td>
<td>ongoing</td>
</tr>
</tbody>
</table>

S = On stable dose of statin
*, P < 0.05; **, P < 0.01; ***, P < 0.001 (pairwise comparisons vs. Placebo)
LSMs and P values from baseline-adjusted ANCOVA model
Placebo subjects completed prior to day 140

*Data reported are from database transfer Sept.24th 2015; Fitzgerald, AHA, November 2015
RNAi Therapeutics for HBV
Efficacy in HBV-Infected Chimpanzees

Dose-dependent antiviral response with intra-subject ascending doses

- Mean 2.9 $\log_{10}$ decrease in viral DNA day 2-6 post 0.5 mg/kg dose
  - >4 $\log_{10}$ reduction in circulating viral DNA achieved in highest titer animal
- Mean 2.0 $\log_{10}$ reduction in HBsAg at 0.5 mg/kg dose
  - Up to 2.3 $\log_{10}$ reduction achieved

*low titer animal dropped below LLOQ from day 23-day 98

Plasma Viral Load (bDNA)

Plasma HBsAg (Surface Antigen)
**ALN-HBV Development Candidate (DC)**

**Potent ESC-GalNAc Conjugate for SC Administration**

**Potent, multi-log HBsAg knockdown in murine model**

- Mouse model with AAV-HBV vector
- ALN-HBV DC achieves potent and highly durable knockdown of HBsAg
  - Up to $3.6 \log_{10}$ HBsAg reduction
  - Single SC dose achieves $>2 \log_{10}$ HBsAg reduction lasting $>30$ days
  - Multiple SC doses achieve $>2 \log_{10}$ HBsAg reduction lasting $>90$ days

![Single SC Dose](image1)

![Multiple SC Doses](image2)

Pre-dose HBsAg titer range ~10-500 ng/mL

Sepp-Lorenzino, *Liver Meeting, November 2015*