This presentation contains forward-looking statements. 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 those that we discuss 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.
RNA Interference (RNAi)
A New Class of Innovative Medicines

RNAi Therapeutics
- Harness natural pathway
  - Catalytic mechanism
  - Mediated by small interfering RNAs or “siRNAs”
- Treat disease with therapeutic gene silencing
  - Any gene in genome
    - Creates unique opportunities for innovative medicines
RNAi Therapeutics

The Time is Now: 3 Reasons

1. Delivery breakthroughs enable clinical translation

2. Growing human experience: safety and predictable PK
   - >500 Subjects/patients enrolled overall
   - Systemic delivery in human trials
     » >70 Patients dosed
     » >225 Doses administered
     » >17 Months of dosing
   - RNAi therapeutics generally well tolerated
   - Pharmacologically relevant human tissue levels achieved

3. Human RNAi proof of mechanism established

![Graph showing TTR mRNA Levels](image1)

**Pre-Clinical Animal Studies**

- Control
- 0.03
- 0.1
- 0.3 mg/kg

**siRNA** (MC3-LNP)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>% Specific cleavage</th>
<th>Evidence of RNAi</th>
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<tr>
<td>Patient A</td>
<td></td>
<td></td>
<td>1.4%</td>
<td>NO</td>
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<tr>
<td>Patient B</td>
<td></td>
<td></td>
<td>29.2%</td>
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<td>Untreated control</td>
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<tr>
<td>untreated control</td>
<td>hepatocellular cancer</td>
<td>0.3%</td>
<td>NO</td>
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<tr>
<td>Untreated control</td>
<td>normal liver</td>
<td></td>
<td>0.1%</td>
<td>NO</td>
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</table>

% Specific cleavage: 27.9%

Evidence of RNAi: YES

p < 0.0001

![RNA cleavage site](image2)

...ATAGGAGATGAGCTTCCTACACAGCACACAAACAATG...

...AGATGAGCTTCCT... CAGCACACAAACA...

Evidence of RNAi: NO

plot location vs. no of reads

Reads/Total Reads

5' Location along mRNA 3'
**RNAi for genetically defined disease as core strategy**

- **5 Products by 2015** in advanced clinical development
- **Product characteristics**
  - Genetically defined target/disease
  - Existing Alnylam delivery platform
  - Early biomarkers in Phase I
  - Clear and rapid development and commercial paths

**Core Programs**
1. ALN-TTR
2. ALN-PCS
3. ALN-HPN
4. ALN-APC
5. TBA

**Partner Programs**
<table>
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<td>Respiratory Syncytial Virus</td>
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<td>Liver Cancers</td>
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<td>ALN-VSP</td>
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<td>Huntington’s Disease</td>
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<td>ALN-HTT</td>
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</table>

**Legend:**
- **Alnylam 5x15 Programs**
- **Partner Programs**
Transthyretin (TTR)-Mediated Amyloidosis (ATTR) Program
Unmet Need and Product Opportunity

RNAi to treat genetic disease

- ATTR is significant orphan disease
  - ~50,000 patients worldwide
- Clinical pathology
  - Onset ~40 to >60 yr
  - Two predominant forms
    - Familial amyloidotic polyneuropathy (FAP)
    - Familial amyloidotic cardiomyopathy (FAC)
  - Peripheral sensorimotor neuropathy, autonomic neuropathy, and/or cardiomyopathy
  - Fatal within 5-15 years
- Liver transplant current standard of care
  - <3,000 Patients eligible
- Recent EU approval of Pfizer’s Vyndaqel™ (tafamidis) for FAP
Mutant TTR is genetic cause of ATTR
- >100 Defined mutations; Autosomal dominant
- Misfolds and forms amyloid deposits in nerves and heart
- Wild-type TTR also accumulates in amyloid plaques
  » Limits benefits of liver transplantation
- Additional validation in mouse genetic models

ALN-TTR in clinical development
- Targets mutant and wild-type TTR
- *In vivo* efficacy established in multiple pre-clinical animal models
- Phase I with ALN-TTR01
- IND for ALN-TTR02 at ~YE ’11
**ALN-TTR Therapeutic Efficacy**

**V30M TTR Transgenic Model**

**ALN-TTR01 treatment results in TTR amyloid regression**
- Treatment paradigm in animals with existing amyloid plaques
- >90% Regression of existing V30M hTTR deposits in peripheral tissues
- Similar animal model data in prevention paradigm

---

**Graph**

- **Relative TTR Tissue Levels**
- **Columns**:
  - Control siRNA
  - ALN-TTR01
- **Tissues**:
  - Esophagus, Colon, Stomach, Sciatic nerve, Dorsal root ganglion
- **Relative Levels**:
  - Esophagus: 100%
  - Colon: 98.8%
  - Stomach: 98.5%
  - Sciatic nerve: 97%
  - Dorsal root ganglion: 98.8%

---

**Int'l Amyloidosis Symp., April 2010**
ALN-TTR01 Phase I Study

Study Design
- Randomized, placebo-controlled, single-blind, single-dose escalation study
  - 3:1 Randomization
  - 4 Patients/cohort
  - 7 Dose groups (0.01-1.0 mg/kg)
- Up to 36 patients with ATTR
  - Conducted in Portugal, Sweden, France and UK

Primary Objective
- Evaluate safety and tolerability of ALN-TTR01

Secondary Objective
- Characterize plasma PK
- Assess preliminary pharmacodynamics and clinical activity
  - Serum TTR, RBP, Vitamin A levels

Study Status
- Dose escalation completed; accruing additional patients at top dose
ALN-TTR01 single dose results in rapid, dose-dependent, and durable lowering of serum TTR protein levels

- All patients show TTR lowering at 1.0 mg/kg, ranging 25-81%
- Average nadir at approximately Day 7 of 41% relative to placebo (geometric mean vs. placebo, p=0.02)
ALN-TTR01 Phase I Study Results
Robust RNAi in Patient at 1 mg/kg ALN-TTR01

- Single 1 mg/kg dose lowers serum TTR protein, RBP and vitamin A levels
- TTR protein reduced by 81% at nadir
- Rapid onset of effect with >50% lowering at day 2
- Nadir at ~day 7
- Durable effect with ~50% lowering at day 28

*Int'l. Symp. FAP, Nov. 2011*
ALN-TTR01 Phase I Summary

Human Proof of Concept for RNAi Therapeutics in ATTR Patients

- ALN-TTR01 is safe and well-tolerated
- Single dose results in rapid, dose-dependent, and durable lowering of serum TTR protein levels
  - At 1.0 mg/kg, all patients show evidence of TTR lowering, with average nadir of 41% relative to placebo at ~day 7 (p=0.02)
- Demonstration of human proof of concept with ALN-TTR01
  - 1st Demonstration of RNAi silencing of disease-causing protein in humans
  - Continued clinical development, including ALN-TTR02 which uses 2nd generation LNP
ALN-TTR02 shows >10-fold improved *in vivo* efficacy in animal models

- ALN-TTR02 uses 2\textsuperscript{nd} generation MC3 LNP formulation
- Single i.v. infusion; Serum TTR levels post-dosing
- Potent, dose-dependent, and durable TTR silencing
- On track to file IND/IND equivalent ~YE '11

*Oligo Ther Soc.*, Sep 2011
RNAi to treat severe hypercholesterolemia

- Elevated LDLc (“bad” cholesterol) is validated risk factor for coronary artery disease and MI
  - Current target level <70 mg/dL
- Significant unmet medical need
  - >500,000 Patients with severe hypercholesterolemia
    - LDLc >200 mg/dL
    - Inadequately managed by statins and other drugs
    - Includes statin intolerant patients
    - At risk for early MI, recurrent MI, death
  - Multiple genetically defined patient subgroups with increasing delineation
    - Defines novel strategies for innovative medicines
PCSK9 Target and ALN-PCS Program

**PCSK9 function well defined**
- PCSK9 (proprotein convertase subtilisin/kexin type 9) expressed predominantly in liver
- Both intracellular and extracellular PCSK9 regulate LDL receptor (LDLr) levels on hepatocytes
  - Increased PCSK9 decreases LDLr levels, elevating plasma LDLc
- Extracellular PCSK9 can be measured in plasma

**PCSK9 genetically defined disease target**

![Graphs showing the relationship between PCSK9 mutation and plasma LDL cholesterol levels and coronary heart disease percentage](image)

*Wild-type PCSK9 (N=3278) vs. Loss of Function PCSK9 Mutation (N=85)*


**ALN-PCS in clinical development**
- Targets both intracellular and extracellular PCSK9
- *In vivo* efficacy established in multiple pre-clinical animal models
- Phase I study initiated Sep. 2011
Like human genetics, RNAi reduces both extracellular and intracellular protein
  » Block feedback loops

RNAi approach has many potential therapeutic advantages
  » Variable levels of extracellular PCSK9 may complicate dosing for Mabs
  » Mab effects on HDL or rebound effects on total cholesterol
  » Potential Mab-induced tachyphylaxis

Alnylam at forefront of major genetic studies providing key competitive advantage
  » UPenn/MGH/Broad Collaboration; UTSW Collaboration

PCSK9 role in both intracellular and extracellular degradation of LDLr

PCSK9 transcription highly sensitive to cholesterol levels and compensates to restore homeostasis

ALN-PCS Pre-Clinical Efficacy Phenocopies Human Genetics

ALN-PCS demonstrates potent efficacy after **single** dose
- Rapid and dose-dependent reduction in PCSK9 protein
- PCSK9 silencing results in >50% reduction in LDLc
- Durable efficacy lasting >30 days
- No decrease in HDL levels

*PCSK9 Conference: From Gene to Therapeutic, Mar 2010*
ALN-PCS Phase I Study

Study Design

- Randomized, placebo-controlled, single-dose escalation study
- ~32 healthy volunteer subjects with elevated baseline LDLc (>116mg/dL)
  - Conducted in UK
- Primary objective
  - Safety and tolerability
- Secondary objectives
  - Characterization of pharmacokinetics
  - Assess preliminary pharmacodynamic activity
    - Plasma PCSK9 protein and LDLc levels
- Treatment regimen
  - Dose levels: 0.015 to 0.25 mg/kg
- Status
  - Phase I trial initiated, September 2011
  - Expect to report human POC data at or around YE’ 11
RNAi to treat hemophilia

- Hemophilias are recessive X-linked monogenic bleeding disorders
  - Hemophilia A defined by loss of function mutations in Factor VIII
    - >40,000 Patients in EU/US
  - Hemophilia B defined by loss of function mutations in Factor IX
    - ~9,500 Patients in EU/US

- Hemophilia A “inhibitor” patients define segment of highest unmet need and cost*
  - ~1/3 Patients with severe hemophilia A
  - >6 Bleeds/patient/year
  - >5 in-hospital days/patient/year
  - >$300,000/patient/year
  - Very poor quality of life

- Only available therapies: rFVIIa (NovoSeven™) and FEIBA
  - Short half-life, requiring frequent dosing
  - Not optimally effective

*Gringeri et al., Blood 2003
Protein C Target and ALN-APC Program

Protein C (PC) is genetically defined target
- Activated Protein C (APC) defines key natural anticoagulant pathway
  » Inactivates factors Va and VIIIa
  » Attenuates thrombin generation
- Heterozygous PC deficiency associated with increased thrombin generation
- Expressed in liver; circulates in plasma

APC Resistance (i.e., Factor V<sub>Leiden</sub>)
- Co-inheritance associated with milder bleeding in hemophilia patients

<table>
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<tr>
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<th>No Co-Inheritance</th>
<th>With Co-Inheritance</th>
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</thead>
<tbody>
<tr>
<td>First bleed age (range)</td>
<td>0.9 (0.1 – 4.0)</td>
<td>1.5 (0.5 – 7.1)</td>
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<tr>
<td>Annual bleeding frequency (range)</td>
<td>6.0 (0 – 30)</td>
<td>1.8 (0 – 7)</td>
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</tbody>
</table>

Kurnik et al., *Hematologica*, 2007

ALN-APC in R2D
- siRNA optimization
- *In vivo* efficacy in pre-clinical animal models
- IND Filing 2013
Refractory Anemia Program
Unmet Need and Product Opportunity

RNAi to treat refractory anemia

- Anemia of chronic disease (ACD) across multiple populations
  - End-stage renal disease (ESRD)
  - Cancer
  - Chronic inflammatory disorders

- Significant unmet need; e.g., ESRD
  - Resistant to high doses of EPO and i.v. iron and poor QOL

- Significant unmet need; e.g., Cancer
  - Anemia in multiple myeloma and MDS

- Additional genetic causes
  - E.g., Iron-refractory iron deficiency anemia (IRIDA)
Hepcidin Pathway and ALN-HPN Program

**Hepcidin pathway is genetically defined**
- Hepcidin is central regulator of iron homeostasis
  - Down-regulates ferroportin
    - Reduces iron uptake by enterocytes
    - Reduces mobilization by macrophages
- Validated in human genetics
  - Mutations in hepcidin and hepcidin pathway
- Expressed in liver, circulates in plasma

**Genetic defects in hepcidin pathway lead to anemia**

<table>
<thead>
<tr>
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<th>Wild type control</th>
<th>TMPRSS6 -/- patient</th>
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<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>14-18</td>
<td>7.9-9.4</td>
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<tr>
<td>Serum Fe (mg/dL)</td>
<td>92-184</td>
<td>12-18</td>
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<tr>
<td>Transferrin saturation (%)</td>
<td>15-45</td>
<td>3.3-4.8</td>
</tr>
</tbody>
</table>

Altamura et al., *Biochem J*, 2010

**ALN-HPN in R2D**
- siRNA optimization for multiple hepcidin pathway targets
- *In vivo* efficacy in pre-clinical animal models
- IND Filing 2012
# Alnylam 5x15™ Programs

## Definable Clinical Paths with Phase I POC

<table>
<thead>
<tr>
<th>Unmet Need</th>
<th>Phase I Serum Biomarkers</th>
<th>Early Development</th>
<th>Advanced Development</th>
</tr>
</thead>
</table>
| **ALN-TTR** | Significant morbidity and mortality 45-60 yrs of age with neuropathy and cardiomyopathy | • TTR  
• Vitamin A  
• Retinol binding protein | Dose/regimen for >50% TTR reduction | FAP: Improvement in neuropathy score (NIS-LL) |
| **ALN-PCS** | Significant morbidity and mortality associated with LDLc >200 mg/dL | • PCSK9  
• LDLc | Dose/regimen for >50% LDLc reduction | LDLc reduction in genetically defined high risk population |
| **ALN-HPN** | Poor QOL and need for blood transfusions, very high EPO and i.v. iron doses | • Hepcidin  
• Iron  
• Hb  
• Transferrin saturation | Dose/regimen for serum hepcidin reduction and increase in Hb | >1 g/dL increase in Hb in refractory anemia patients |
| **ALN-APC** | Significant bleeding, hospitalizations, and costs associated with severe hemophilias, including “Inhibitor” pts | • Protein C  
• Thrombin generation  
• Thromboelastography | Dose/regimen to normalize thrombin generation | Reduced #bleeds over 6-12 mo period |
Partner Programs

Respiratory Syncytial Virus
- Significant unmet medical need
  » >125,000 Pediatric hosp./yr in US
  » >170,000 Adult hosp./yr in US
- No effective therapies to treat RSV

Liver Cancer
- Prevalent solid tumor and common site of metastatic disease
  » ~700,000/yr Incidence of HCC worldwide
  » ~500,000/yr Patients with liver mets

Huntington’s Disease
- Significant inherited neurodegenerative disease
  » Caused by mutations in huntingtin gene
  » 30,000 US patients; 150,000 with 50% risk

ALN-RSV01
- Targets key viral gene blocking replication
- Phase IIb RSV-infected lung transplant patient study ongoing
  » Enrollment complete; ~90 patients
  » Data in mid-2012
- 50-50 US Partnership with Cubist
- Partnered with Kyowa in Asia

ALN-VSP
- Targets two distinct genes involved in cancer pathways
  » KSP for proliferation; VEGF for angiogenesis
- Phase I liver cancer study completed
  » Results reported at ASCO 2011
    - ALN-VSP generally well-tolerated
    - 41 Patients; ranging from 0.1 - 1.5mg/kg
    - Recommended Phase II dose is 1.0 mg/kg q2w
    - 3 Patients on extension study
  » Demonstrated both clinical activity and RNAi POM
    - 64% Disease control at Phase II dose
    - 1 PR in endometrial cancer patient
    - RNAi demonstrated in biopsy samples
- Partner prior to Phase II

ALN-HTT
- Targets huntingtin gene
- Pre-clinical development
  » IND candidate 2012
- Drug-Device collaboration with CHDI and Medtronic
  » Alnylam/Medtronic 50/50 in U.S
  » 50% funding from CHDI
RNAi Technologies and New Ventures

Bioprocessing/Biologics

Genomics

Stem Cells

microRNA Therapeutics

Vaccines

Other Non-Coding RNAs (e.g., RNAa)
2011 Q3 Financial Results

- Cash ~$286M
  - ~$6.70 per share
- GAAP Revenues ~$21M
  - Roche, Takeda, and other licenses
- GAAP Operating Expenses ~$33M
  - Includes non-cash stock-based compensation charges of ~$4M
- Shares Outstanding ~43M

2011 Guidance

- Year-end Cash >$250M
## Pipeline Goals 2011-2012

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<th>Program</th>
<th>R2D</th>
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<th>Phase I Human POC</th>
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### Additional Corporate Goals 2011

- Additional partnerships
- Year-end cash >$250M
Thank You

www.Alnylam.com