RNAi Roundtable: ALN-AAT for the Treatment of Alpha-1 Antitrypsin Deficiency-Associated Liver Disease

August 20, 2014
Welcome

- Josh Brodsky
  Manager, Investor Relations and Corporate Communications

Introduction

- Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President and Chief Medical Officer

Overview of Alpha-1 Antitrypsin Deficiency

- David Brenner, M.D., Vice Chancellor for Health Sciences and Dean of the
  School of Medicine at the University of California, San Diego

Q&A Session

- with Dr. Brenner

ALN-AAT Program

- Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development

Q&A Session
Reminders

• Event will run until ~1:30 p.m. ET
• Q&A session at end of each presentation
  » Submit questions at bottom of webcast screen
  » Questions may be submitted at any time
• Replay, slides, and audio available at www.alnylam.com
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 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.
Welcome
- Josh Brodsky
  Manager, Investor Relations and Corporate Communications

Introduction
- Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President and Chief Medical Officer

Overview of Alpha-1 Antitrypsin Deficiency
- David Brenner, M.D., Vice Chancellor for Health Sciences and Dean of the School of Medicine at the University of California, San Diego

Q&A Session
- with Dr. Brenner

ALN-AAT Program
- Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development

Q&A Session
**Alnylam 5x15™ Strategy**

**A Reproducible and Modular Path for Genetic Medicines**

1. **Liver-expressed target gene**
   - Involved in disease with high unmet need
   - Validated in human genetics
   - GalNAc-siRNA enables SC dosing with wide therapeutic index

2. **POC achieved in Phase 1**
   - Blood-based biomarker with strong disease correlation
     - e.g., Serum TTR, thrombin generation, hemolytic activity, LDL-C, HBsAg levels

3. **Definable path to approval and market**
   - Established endpoints
   - Focused trial size
   - Large treatment effect
   - Collaborative approach with physicians, regulators, patient groups, and payers
<table>
<thead>
<tr>
<th>Category</th>
<th>Discovery</th>
<th>Development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR-Mediated Amyloidosis</td>
<td>ALN-TTRsc</td>
<td>Patisiran (ALN-TTR02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemophilia and Rare Bleeding Disorders</td>
<td>ALN-AT3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement-Mediated Diseases</td>
<td>ALN-CC5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Porphyrias</td>
<td>ALN-AS1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>ALN-PCSsc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-1 Antitrypsin Deficiency</td>
<td>ALN-AAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B Virus Infection</td>
<td>ALN-HBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-Thalassemia and Iron-Overload Disorders</td>
<td>ALN-TMP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Hyperlipidemia and Hypertriglyceridemia</td>
<td>ALN-ANG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>ALN-AC3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional Genetic Medicine and Other Programs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Delivery Technology: LNP (IV) Standard Template Chemistry (STC)-GalNAc Conjugate (SC) Enhanced Stabilization Chemistry (ESC)-GalNAc Conjugate (SC)*
## Alnylam Development Pipeline

<table>
<thead>
<tr>
<th>Category</th>
<th>Discovery</th>
<th>Development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR-Mediated Amyloidosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patisiran (ALN-TTR02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALN-TTRsc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemophilia and Rare Bleeding Disorders</td>
<td></td>
<td>ALN-AT3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement-Mediated Diseases</td>
<td></td>
<td>ALN-CC5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Porphyrias</td>
<td></td>
<td>ALN-AS1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td></td>
<td>ALN-PCSsc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-1 Antitrypsin Deficiency</td>
<td>ALN-AAT</td>
<td></td>
<td></td>
<td></td>
<td>IND filing mid '15</td>
</tr>
<tr>
<td>Hepatitis B Virus Infection</td>
<td></td>
<td>ALN-HBV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-Thalassemia and Iron-Overload Disorders</td>
<td></td>
<td>ALN-TMP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Hyperlipidemia and Hypertriglyceridemia</td>
<td></td>
<td>ALN-ANG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td></td>
<td>ALN-AC3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional Genetic Medicine and Other Programs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Delivery Technology:**
- LNP (IV)
- Standard Template Chemistry (STC)-GalNAc Conjugate (SC)
- Enhanced Stabilization Chemistry (ESC)-GalNAc Conjugate (SC)
Alnylam IP for AAT-Directed RNAi Therapeutics

**Broad siRNA IP**
- Includes Tuschl, McSwiggen, and Kreutzer-Limmer patent families
  - Claims cover siRNA architecture and chemical modifications
  - siRNA lengths from 15 to 49 nts
  - Independent of sequence or target
- Today’s Tuschl ’262 patent allowance
  - Covers double-stranded molecules with up to 25 base pairs and one or more nucleotide analogues
    - Includes “dicer substrate” siRNA and use of “unlocked nucleobase analogues” or “UNA”

**Delivery and Target siRNA IP**
- Includes Manoharan patent family covering GalNAc-conjugates
- Includes target-specific filings on RNAi therapeutics targeting AAT
  - Early filing given Alnylam’s pioneering of this application
Welcome
- Josh Brodsky
  Manager, Investor Relations and Corporate Communications

Introduction
- Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President and Chief Medical Officer

Overview of Alpha-1 Antitrypsin Deficiency
- David Brenner, M.D., Vice Chancellor for Health Sciences and Dean of the School of Medicine at the University of California, San Diego

Q&A Session
- with Dr. Brenner

ALN-AAT Program
- Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development

Q&A Session
Alpha-1 antitrypsin liver diseases

David A. Brenner, M.D.
Vice Chancellor, Health Sciences
Dean, School of Medicine

UC San Diego
Health Sciences
International
Apha-1 antitrypsin (a1AT)

- Abundant glycoprotein product mainly synthesized by hepatocytes and secreted into the blood
- Inhibits neutrophil protease, thus preventing damage to the pulmonary architecture.
- Increased production as acute phase reactant to stress
Genetics of a1AT Deficiency

Alleles:
- M – Wild-type
- Z – classic mutant in which Lys342Glu
- S – rare mutant, less polymerization

Genotypes:
- MM – Wild-type
- MZ – Z heterozygous, modifies liver disease
- MS – S heterozygous, no liver disease
- SZ – compound heterozygous, associated with liver disease
- ZZ – classic a1AT deficiency
Prevalence of alpha-1 antitrypsin deficiency

- M or wild type accounts for 95% of alleles in white Americans
- ZZ – 1 in 3500 births, more common in Caucasians
- Z heterozygous – 14 per 1000 in Caucasians, 2.6 in Hispanics, and 2.6 in African Americans.
a1AT Pediatric Liver Disease

- In infancy – neonatal cholestasis (neonatal hepatitis syndrome). 80% are healthy at 18 y.o.
- Swedish study in 1970s – risk of life-threatening liver disease 3-5%, risk of abn LFTs – 15-60%.
- Liver bx – variable PAS+ a1AT mutant Z protein.
- Older children – rarely present with failure to thrive, hepatomegaly, cirrhosis.
a1AT Adult Liver Disease

- Natural History largely known from Swedish population studies.
- In early adulthood, most PiZZ patients have normal liver function tests (perhaps have subclinical liver injury).
- 37% of adult PiZZ patients have cirrhosis at autopsy.
- 30% of PiZZ patients with cirrhosis have hepatocellular cancer at autopsy.
- Standard LFTs are not a sensitive method to detect liver injury.
The autophagic pathway

Pathways for degradation of mutant ATZ accumulating in the endoplasmic reticulum (ER).

Use of the GFP-LC3 mouse to assay for activation of hepatic autophagy.

Model for the putative role of RGS16 in activating autophagy in liver cells that accumulate mutant ATZ.

Hepatocellular proliferation in the PiZ mouse model of AT deficiency.

Perlmutter DH. 2011.
Annu. Rev. Med. 62:333–45
Alpha-1 antitrypsin Z protein (PiZ) increases hepatic fibrosis in a murine model of cholestasis
Alpha-1 antitrypsin Z protein (PiZ) increases hepatic fibrosis in a murine model of cholestasis
Rationale and Options for a1AT testing

• It is important to test for a1AT deficiency in all patients diagnosed with liver disease of unexplained etiology or those with a family history of liver disease.

• Also test patients with COPD, adults with asthma that does not reverse with maximal medical therapy, and all family members of those diagnosed with a1AT deficiency.
Laboratory tests used to confirm a diagnosis of a1AT

- measurement of AAT serum or plasma protein levels – usually PiZZ <50% of normal.
- A1AT protein phenotyping – isoelectric focusing, may miss heterozygotes.
- A1AT genotyping – PCR to identify common genetic variants, identifies heterozygotes.
Implications for patients with a1AT ZZ

• Assessment of liver function (AST, ALT, albumin, PT)
• Pulmonary function testing (spirometry)
• Smoking cessation in smokers is recommended and smoking initiation in non-smokers is discouraged
• Liver biopsy is not typically required to diagnose AAT-related liver disease
The association between heterozygosity of alpha 1-antitrypsin deficiency alleles and the risk of developing chronic liver disease remains controversial.

Increased prevalence of the PiMZ heterozygous state in patients with cirrhosis.

Association between the PiMZ heterozygous state and increased severity of liver disease.

The liver of PiMZ patients contain the characteristic PAS-positive diastase-resistant inclusions of a1AT deficiency, but fewer than the PiZZ patients.

the PiMS and PiSS phenotypes do not contribute to liver disease.
Relationship between alpha-1 antitrypsin deficiency and HCC

- a1AT deficiency is associated with an increased risk of HCC.
- almost exclusively confined to those patients with cirrhosis associated with the Z allele and a1AT deficiency.
- The risk appears to increase with age and male gender.
- It has been suggested that the heterozygous state may serve as a risk modifier or multiplier in patients with other underlying causes of liver diseases.
Recommendations for screening for hepatocellular cancer (HCC)

• The American Association for the Study of Liver Disease (AASLD) recommends that patients with cirrhosis due to a1AT deficiency be screened for HCC
• Guidelines calls for regular screening using ultrasound examination of the liver every 6 months
• There does not appear to be a basis for recommending routine surveillance for patients with a1AT deficiency who do not have significant liver disease or cirrhosis
Liver Transplantation

- Patients with a1AT deficiency who develop decompensated cirrhosis or early-stage hepatocellular carcinoma
- Liver transplantation both replaces the diseased liver and corrects the underlying metabolic disorder
- Both graft and patient survival for this metabolic disease is similar to that of other indications for transplant
- 83% survival for adults with A1TZ at 5 year.
- Preliminary results report that liver transplantation may prevent or slow the progression of pulmonary disease in patients with a1AT deficiency.
Welcome
• Josh Brodsky
  Manager, Investor Relations and Corporate Communications

Introduction
• Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President and Chief Medical Officer

Overview of Alpha-1 Antitrypsin Deficiency
• David Brenner, M.D., Vice Chancellor for Health Sciences and Dean of the
  School of Medicine at the University of California, San Diego

Q&A Session
• with Dr. Brenner

ALN-AAT Program
• Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development

Q&A Session
Welcome
- Josh Brodsky
  Manager, Investor Relations and Corporate Communications

Introduction
- Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President and Chief Medical Officer

Overview of Alpha-1 Antitrypsin Deficiency
- David Brenner, M.D., Vice Chancellor for Health Sciences and Dean of the School of Medicine at the University of California, San Diego

Q&A Session
- with Dr. Brenner

ALN-AAT Program
- Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development

Q&A Session
Therapeutic Hypothesis for ALN-AAT

Z-AAT mRNA expression in hepatocytes

Misfolded Z-AAT protein aggregates in hepatocytes forming polymers

Z-AAT polymers cause hepatocyte damage

Results in liver fibrosis and HCC
Therapeutic Hypothesis for ALN-AAT

- Z-AAT mRNA expression in hepatocytes
- Reduced Z-AAT polymers in hepatocytes
- Reduced hepatocyte damage
- Decrease in liver fibrosis and HCC

ALN-AAT

GalNAc$_3$
GalNAc-siRNA Conjugates
Subcutaneous Delivery of RNAi Therapeutics

Asialoglycoprotein Receptor (ASGPR)
- Highly expressed in hepatocytes
- High rate of uptake
- Recycling time ~15 minutes
- Conserved across species

GalNAc-siRNA Conjugates
- siRNA conjugated to N-acetylgalactosamine (GalNAc) ligand
- Efficient delivery to hepatocytes following subcutaneous administration
- “Enhanced stabilization chemistry” (ESC) used with ALN-AT3, ALN-PCSsc, ALN-CC5, ALN-AS1, ALN-AAT, and future programs
  » Significantly improved potency and durability compared with ALN-TTRsc
Effective Z-AAT Knockdown in Fibrotic Liver

Experiment Hypothesis

- Transgenic human Z-AAT expressing mice develop liver tumors with age
- Can chronic dosing in aged mice with fibrotic livers decrease the tumor incidence?

Decrease in Liver mRNA; Individual Animals

Serum AAT After First Injection

Sehgal, Digestive Disease Week, May 2014
In Collaboration with J Teckman, St Louis
Z-AAT Knockdown Reduces Polymer Formation

PAS Globule Staining

AAT Globules

Relative Globule Area

PBS

AAT-siRNA

$p=0.02$
Z-AAT Knockdown Improves Liver Physiology

Decrease in Fibrosis

\[ \text{Relative Col1a2 mRNA Levels} \]

\[ \text{PBS} \quad 1.2 \quad 1.0 \quad 0.8 \quad 0.6 \quad 0.4 \quad 0.2 \quad 0.0 \]

\[ \text{AAT-siRNA} \]

\[ p=0.04 \]

Decrease in Immune Cells

\[ \text{Relative PTPRC mRNA Levels} \]

\[ \text{PBS} \quad 1.1 \quad 1.0 \quad 0.9 \quad 0.8 \quad 0.7 \quad 0.6 \quad 0.5 \]

\[ \text{AAT-siRNA} \]

\[ p=0.002 \]
Z-AAT Knockdown Reduces Tumor Formation

**Tumor Incidence**
- 4/6 PBS animals had liver tumors
- 1/6 AAT treated animals had liver tumor

<table>
<thead>
<tr>
<th>Tmt</th>
<th>An #</th>
<th>Observation (p=0.045)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td>A</td>
<td>No macroscopic tumor</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>large tumor in left lateral lobe, ~5mm diameter</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>2mm tumor in caudate lobe, many lesions in 2nd aux lobe</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1.5mm tumor in caudate lobe, 1mm lesion in right medial lobe, multiple 1mm lesions in 1st aux lobe</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>3mm tumor in left lateral lobe</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>No macroscopic tumor</td>
</tr>
<tr>
<td>AAT-siRNA</td>
<td>A</td>
<td>No macroscopic tumor</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>3mm tumor in caudate lobe</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>No macroscopic tumor</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>No macroscopic tumor</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>No macroscopic tumor</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>No macroscopic tumor</td>
</tr>
</tbody>
</table>

**Proliferating Cells**

- **PBS**
  - Relative BrdU Count: 1.2
- **AAT-siRNA**
  - Relative BrdU Count: 0.4

Sehgal, *Digestive Disease Week*, May 2014
Therapeutic Hypothesis Confirmed
Summary

• Z-AAT knockdown leads to
  » Reduction in PAS globules and AAT polymers
  » Reduction of hepatic fibrosis markers
  » Decrease in proliferative index
  » Decrease in hepatic tumor incidence

• Chronic dosing can decrease disease burden
• In addition, results demonstrate efficient and robust delivery to fibrotic livers of aged animals
ALN-AAT Candidate Selection in Mice
Duration, Dose Response and Repeat Dosing

Screening AAT-siRNA Candidates *In Vivo*

Single Dose Efficacy: Dose Response

ED50 ~ 0.5mg/kg

Single Dose: Dose Response and Duration

Multi-Dose at 0.5mg/kg, BIW

Sehgal, *Digestive Disease Week*, May 2014
ALN-AAT Development Candidate in NHP
Initial Pre-Clinical Results

Ongoing Study in NHPs

- Single doses at 1.0 and 3.0 mg/kg
- Repeat dose at 1mg/kg Q1W
  - N=3
  - Serum AAT by ELISA
- Well tolerated
  - No safety findings
  - No change in cytokines
  - No injection site reactions
- Rapid, potent AAT knockdown
  - Single dose ED$_{50}$ < 1 mg/kg
  - Comparable single dose potency with other ESC-GalNAc-siRNA conjugates
    - Multi-dose ED$_{80}$ < 1 mg/kg
    - Expect ~10-fold lower doses and greater durability in human

Serum AAT Levels

<table>
<thead>
<tr>
<th>Days</th>
<th>1mg/kg SD</th>
<th>3mg/kg SD</th>
<th>1mg/kg q1w</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td><img src="#" alt="Graph" /></td>
<td><img src="#" alt="Graph" /></td>
<td><img src="#" alt="Graph" /></td>
</tr>
</tbody>
</table>

% Mean Serum AAT Knockdown (Relative to Baseline)
ALN-AAT Commercial Opportunity

Significant potential for disease modifying therapy addressing underlying cause of PiZZ liver pathology

- Orphan disease with substantial morbidity and mortality
  - Liver transplant is only option, limited to small population
- Potential for rapid penetration
  - Significant number of patients already diagnosed
  - Concentrated in centers of excellence
- Value supported by pharmacoeconomics
- Strong patient advocacy, supportive of drug development
  - Includes Alpha 1 Foundation
Potential Target Patient Segments

Significant number of patients with PiZZ liver disease

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Total Population</th>
<th>ALN-AAT Initial Opportunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-1 Antitrypsin Deficiency Patients with PiZZ Mutation</td>
<td>210K</td>
<td></td>
</tr>
<tr>
<td>Adult Patients with Liver Disease</td>
<td>21K</td>
<td></td>
</tr>
<tr>
<td>Pediatric Patients with Liver Manifestations</td>
<td>11K</td>
<td></td>
</tr>
</tbody>
</table>
## Clinical Development Plan

**ALN-AAT for the Treatment of AAT-Deficiency Associated Liver Disease**

### Development plan to maximize product opportunity

<table>
<thead>
<tr>
<th>Phase 1/2</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Healthy Volunteers and PiZZ Patients</td>
<td>Adult PiZZ Patients with Liver Disease, Pre-Cirrhosis</td>
<td>OLE Adult PiZZ Patients with Liver Disease</td>
</tr>
<tr>
<td>Key Objectives:</td>
<td>Key Objectives:</td>
<td>Key Objectives:</td>
</tr>
<tr>
<td>• Safety, PK and Clinical Activity (AAT lowering in serum)</td>
<td>• Clinical Activity (Decreased liver Z-AAT, improved liver physiology and stable histopathology)</td>
<td>• Adult PiZZ Patients with Liver Disease</td>
</tr>
<tr>
<td>• Initial Dose Finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Z-AAT lowering in liver in patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult PiZZ Patients with Liver Disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pediatric PiZZ Patients with Liver Disease</td>
</tr>
</tbody>
</table>
ALN-AAT demonstrates robust efficacy in pre-clinical studies

- ALN-AAT treatment leads to sustained knockdown of AAT → improved liver outcomes
- Repeat dose ED$_{80}$ <1mg/kg SC in NHPs
  - Expect monthly SC doses <1 mg/kg in humans (< 1mL/injection)
- Wide therapeutic index based on initial safety studies

On-track for mid ’15 IND filing

- Expect Phase 1 start in mid ’15
- Employs clinically validated ESC-GalNAc platform
- Will become 7$^{th}$ clinical program in Alnylam’s expanded “5x15” product strategy

ALN-AAT represents significant commercial opportunity

- Orphan disease with high unmet need for disease-modifying therapy

Clinical development plan to maximize product opportunity
Welcome
• Josh Brodsky
  Manager, Investor Relations and Corporate Communications

Introduction
• Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President and Chief Medical Officer

Overview of Alpha-1 Antitrypsin Deficiency
• David Brenner, M.D., Vice Chancellor for Health Sciences and Dean of the School of Medicine at the University of California, San Diego

Q&A Session
• with Dr. Brenner

ALN-AAT Program
• Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development

Q&A Session
Next RNAi Roundtable

ALN-AS1 for the treatment of Hepatic Porphyrias

*Thursday, August 21 @ 4:00 p.m. – 5:00 p.m. ET*

- Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development
- Moderator: Barry Greene, President and Chief Operating Officer
- Guest Speaker: Karl Anderson, M.D., FACP, Professor, Departments of Preventive Medicine and Community Health (Division of Human Nutrition) and Internal Medicine (Division of Gastroenterology), and Director, Porphyria Laboratory & Center at the University of Texas Medical Branch

Replays of previous RNAi Roundtables available at www.alnylam.com/capella
Select Scientific and Clinical Meetings
Mid to Late ’14

- High Blood Pressure Research (HBPR)
  » September 9-12, San Francisco, CA

- International Complement Society Workshop (ICSW)
  » September 14-18, Rio de Janeiro, Brazil

- American Neurological Association (ANA)
  » October 12-14, Baltimore, MD

- Oligonucleotide Therapeutics Society (OTS)
  » October 12-15, San Diego, CA

- AASLD (The Liver Meeting)
  » November 7-11, Boston, MA

- American Heart Association (AHA)
  » November 15-19, Chicago, IL

- Venue TBD
  » November

- American Society of Hematology (ASH)*
  » December 6-9, San Francisco, CA

* Pending acceptance of abstracts
Speaker Biographies

Akshay Vaishnaw, M.D., Ph.D.
Executive Vice President and Chief Medical Officer, Alnylam Pharmaceuticals, Inc.
Dr. Vaishnaw joined Alnylam in 2006, coming from Biogen, Inc. (now Biogen Idec Inc.), where he was most recently Senior Director, Translational Medicine. In his seven years at Biogen he was involved in many aspects of clinical research and business development, and led the effort for the approval of alefacept (Amevive™) for psoriasis. Akshay received his M.D. from the University of Wales College of Medicine, U.K., with Distinctions in Pathology and Medicine, and his Ph.D. from the University of London, U.K., in Molecular Immunology. He is a Member of the Royal College of Physicians, U.K. In addition, Akshay has published papers in leading scientific journals and authored a number of textbook chapters relating to autoimmune disease.

David Brenner, M.D.
Vice Chancellor for Health Sciences and Dean of the School of Medicine at the University of California, San Diego
David Brenner, M.D. is Vice Chancellor for Health Sciences and Dean of the School of Medicine at the University of California, San Diego. In this role, Dr. Brenner leads the UC San Diego School of Medicine, Skaggs School of Pharmacy and Pharmaceutical Sciences, UCSD Medical Center, and UCSD Medical Group. Dr. Brenner is a leader in the field of gastroenterological research, specializing in diseases of the liver. He is widely respected as a translational scientist whose work bridges the laboratory and clinical settings. He has focused on understanding the molecular pathogenesis of fibrotic liver disease and the genetic basis of liver disorders as the foundation for improving prevention and treatment of liver disease. For five years he was Editor-in-Chief of Gastroenterology, the premier journal in the field. Dr. Brenner earned his M.D. from the Yale University School of Medicine. Dr. Brenner’s professional memberships include the American Society for Clinical Investigation; the Association of American Physicians, for which he is the secretary; the American College of Physicians; the American Gastroenterological Association, for which he is chair of the Research Policy Committee; and the American Clinical and Climatological Association. He is also on the board of directors of two philanthropic foundations – the AlphaOne Foundation and the Alcoholic Beverage Medical Research Foundation – and serves on numerous editorial boards.

Rachel Meyers, Ph.D.
Vice President, Research and RNAi Lead Development, Alnylam Pharmaceuticals, Inc.
Dr. Rachel Meyers is Vice President of Research and RNAi Lead Development (RLD) at Alnylam. In this capacity, she plays a key role in the advancement of Alnylam’s RNAi therapeutic programs, from early discovery through clinical development and her team is responsible for program leadership for most of Alnylam’s preclinical and clinical stage programs. In addition to leading the research organization, Dr. Meyers has worked closely with Alnylam’s business development group, playing an integral part in establishing important collaborations, and has functioned as a scientific lead in collaborations with Novartis, Takeda, Isis, Roche and Genzyme. She also led the scientific diligence resulting in Alnylam’s acquisition of the Sirna assets from Merck. Prior to taking on the leadership of the Research and RLD Groups, Dr. Meyers was one of Alnylam’s Research Directors, focusing her efforts on the development of RNAi therapeutics to target infectious diseases, and was the project lead for the company’s RSV program, where she was responsible for advancing ALN-RSV01 from inception, through pre-clinical development and into the clinic. Dr. Meyers was honored by Mass High Tech as one of 10 Women to Watch 2007 and by R & D Directions as one of its Top 20 Scientists 2007. Before joining Alnylam in April of 2003, Dr. Meyers was a Senior Scientist at Millennium Pharmaceuticals (1999-2003) where she was involved in the bioinformatics, molecular and cell biology of target discovery. Dr. Meyers completed her postdoctoral training at Harvard Medical School in the field of signal transduction, and received her Ph.D. from MIT in the field of in vitro transcription.
Thank You

www.alnylam.com