ALN-AAT, an Investigational RNAi Therapeutic for the Treatment of Alpha-1 Antitrypsin Deficiency-Associated Liver Disease

August 14, 2015
Agenda

Welcome
• Joshua Brodsky
  Senior Manager, Investor Relations and Corporate Communications

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

Overview of AAT Deficiency-Associated Liver Disease
• Jeffrey Teckman, M.D., Professor of Pediatrics and Biochemistry, St. Louis University School of Medicine

Q&A Session
• With Dr. Teckman

ALN-AAT Program
• Alfica Sehgal, Ph.D.
  Principal Scientist, Research

Q&A Session
Reminders

- Event will run for approximately 60 minutes
- 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
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 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.
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Q&A Session
Alnylam RNAi Therapeutics Strategy
A Reproducible and Modular Path for Innovative 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
## 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>
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Q&A Session
Alpha-1-Antitrypsin

• Abundant serum protein, primarily synthesized in the liver.

• Functions to inhibit neutrophil proteases to protect host tissues during inflammation.
Alpha-1-Antitrypsin Mutant Z

• The mutant associated with the vast majority of liver disease.

• A point mutation encoding aa substitution.

• Homozygous ZZ (“PIZZ”) is the classical form; 1 in 2,000-3,500 births in North America and Europe.
Model of α1AT protein processing in the ER of Hepatocytes

Wild Type M
- Synthesis
- Secretion
- Degradation

Mutant Z
- Synthesis
- Secretion
- Degradation
How Alpha-1 Causes Damage

• **Liver;** Accumulation of mutant Z protein damages liver cells.

• **Lung;** “Deficient” serum level leaves host tissues susceptible to damage by neutrophil proteases. Exquisitely susceptible to smoking injury.
Human ZZ Liver

H&E

PAS with Digestion
ATZ Liver Injury Cascade

a1ATZ synthesis

\[ \text{Secretion to serum} \leftarrow \] a1ATZ ER retention \[ \rightarrow \] ERAD proteolysis

? \[ \rightarrow \] ?

\[ \downarrow \]

a1ATZ polymerization \[ \rightarrow \] autophagy

Heterogeneous hepatic polymer accumulation

Apoptosis in hepatocytes with the largest polymer burden

Caspase activation, mitochondrial depolarization and autophagy

Genetic and Environmental modifiers

Cell death

Hepatocytes with low polymer proliferate to maintain liver mass

Chronic regenerative stimulus

Chronic hepatocellular death and regeneration leads to fibrosis and HCC

Liver Death
Clinical ZZ Liver Disease has a Bimodal Age Distribution

• Infancy and childhood:
  – The natural history of childhood ZZ liver disease is relatively well understood, since most present with biochemical abnormalities leading to diagnosis and follow up

• Older adults:
  – Often silent disease, so natural history less well understood

• Young and middle adult years:
  – Progressive liver disease is likely rare
Swedish Newborn Screening Study
Elucidated Childhood ZZ Liver Disease

127 ZZ newborns identified out of 200,000 screened

- **Neonatal period**
  - 22 (16%) cholestasis
  - 53 (42%) high ALT
  - 52 (42%) normal

  - 15/18 normalized

- **Adulthood**
  (f/u may not be complete)

  - 4 died in infancy;
    - 2 of liver failure
  - All 4 had severe fibrosis

  - Likely not diagnosed
    - Outside screening

No further deaths or evidence of portal hypertension
- 116/127 (91%) normal ALT age 18 years, but not clear later life
- In the last 20 years systemic examination minimal, no ultrasounds
Spectrum of Pediatric ZZ liver Disease

• Risk of life threatening liver disease in childhood is about 5%.

• Risk of any liver disease or dysfunction in childhood is 15-50% (depends on how it is tested).

• The majority (80%?) of ZZ infants with problems at birth are well, without transplant, at age 18y.

• Asthma, but not emphysema is seen in children
Autopsy Study, Sweden

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<th>Smokers (22)</th>
<th>Never-smokers (15)</th>
<th>All (37)</th>
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<td>Cirrhosis</td>
<td>2* p&lt;0.001</td>
<td>11**</td>
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<td>Hepatocellular carcinoma</td>
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<td>Fibrosis</td>
<td>4</td>
<td>0</td>
<td>4</td>
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<tr>
<td>Steatosis</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Normal</td>
<td>14</td>
<td>3</td>
<td>17</td>
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*In one case alcohol + hemochromatosis
Hepatitis B and C markers absent
** Severe, refractory encephalopathy in two.
Prevalence and Spectrum of Adult ZZ liver Disease

• The Swedish autopsy study suggests the majority of never smokers may develop serious liver disease
• A study of patients attending a ZZ pulmonary clinic in the UK found liver disease in 67%
• The spectrum of liver disease in adults ranges from mild fibrosis to frank cirrhosis with portal hypertension
• Complications include liver failure, GI bleeding and hepatocellular carcinoma
Liver Management

• Blood tests alone cannot identify or predict the presence of severe liver disease.

• Severe liver disease can develop with few if any symptoms.

• Careful history, physical exam and a range of tests monitor the liver.

• Current therapy is supportive, with liver transplantation when indicated
Unanswered Questions

• What are the mechanisms of liver damage?
  – Better understanding may suggest novel therapeutic approaches

• What is the true prevalence and variability of ZZ liver disease in adults?
  – Ongoing natural history studies will help to address this

• What are the sources of clinical variability; genetic vs. environment or both?
Research Tools

• In vitro systems.

• Animal models
  – Transgenic “PiZ” mouse; globules, inflammation, proliferation/dysplasia.

• Natural History studies in adults and children
  – Research studies, registry, DNA & tissue bank.
  – Patient community highly motivated
Adult Liver Genetic Linkage Study

• The first multi center, prospective natural history study of adult ZZ liver disease
• Phase I: >100 ZZ adults
• 5 years with liver biopsy at start and finish
• Analysis of specimens at 5 leading academic sites (special chemistry and genetics).
• Information provided to the patients and the scientists.
Additional Studies in Adult ZZ Liver Disease

• Adult Liver Study U of Florida
  – Biopsy study and genetic analysis.
• Arrowhead Research Inc.
  – Pending studies
• Alnylam Pharmaceuticals, Inc.
  – Pending studies
• U Pitt drug study for severe fibrosis.
Natural History of Childhood ZZ Liver Disease: NIH Multi-Center Study in US

http://childrennetwork.org
ChiLDREN: The Childhood Liver Disease Research and Education Network

• NIH-sponsored consortium focused on the study of pediatric liver diseases
• 16 North American tertiary care centers
• LOGIC study includes 400 ZZ patients, age 0-25y, followed prospectively
• Clinical data and annotated biorepository
• Opportunities available for academic and industry collaborations, including treatment trials
Alpha-1-Antitrypsin Deficiency

• A common condition among “rare diseases.”

• 200,000-300,000 patients in US and Europe.

• Liver therapy is an unmet need.

• Good scientific and patient resources to support therapeutic development.
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Q&A Session
Alpha-1 Antitrypsin (AAT)

AAT is serine proteinase inhibitor (serpin)
• Inhibits neutrophil elastase, trypsin, thrombin, chymotrypsin, etc.
• Abundant plasma protein, primarily synthesized in hepatocytes

AAT deficiency
• PiZZ accounts for 95% of AAT-deficient patient population
  ◦ Z allele has point mutation Glu342Lys
    → Slows rate of protein folding
    → Accumulation of an intermediate that polymerizes
    ◦ Reduced secretion
      → Polymer formation
      → Plasma deficiency “Loss of function”
      → Accumulation in hepatocytes “Toxic gain of function”
Lung Disease Liver Disease
Accumulation of Mutant Z-AAT in Liver Causes Disease

Globules of AAT

PAS Staining

Immunostaining

EM

Normal

X 3000

X 12000

Inclusions in ER

Hepatology (2005): 41:160
GalNAc-siRNA Conjugates
Subcutaneous Delivery of Investigational 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
ASGPR is Qualitatively Similar Between Normal and PiZZ Patients

ASGPR Staining (red)

- Normal
- PiZZ Patient

Fibrotic Area

- ASGPR1 or ASGPR2 Immunostaining
- Blue: DAPI/Nuclear Stain
- Human liver tissues
Effective Z-AAT Knockdown in Fibrotic Livers in Tg-PiZ Mice

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?

First SC Dose

6-11 month old animals

Day 0 14 28 42 56 70 84 98 112 126 132  
Sac

PAS Globule Staining

PBS

AAT-siRNA

Globule Area

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<th>Relative Globule Area</th>
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<td>PBS</td>
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<tr>
<td>AAT siRNA</td>
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0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6  
Globule Area

PBS

AAT siRNA
Z-AAT Knockdown Improves Liver Histology and Decreases Tumor Burden in Tg-PiZ Mice

PBS Treated Animal

AAT-siRNA Treated Animal

Nucleus

Relative BrdU Count

Proliferating Cells

$\text{Number of Tumors}$

PBS

AAT siRNA

Count

Tumor Incidence

Tumor Size

PBS

AAT siRNA

Size in mm

$p=0.02$
ALN-AAT Leads to Dose-dependent, Durable, Reduction of Z-AAT in Transgenic Mice

Experiment Design
• Tg-PIZ mice age at dosing = 11±1.6 wks
• N=4, single subcutaneous dose on Day 0
• Weekly bleeds to measure human serum AAT

Results
• Durable, dose dependent silencing
• ED\textsubscript{50} ~0.5 mg/kg
Cumulative, Dose-dependent AAT Knockdown
Ongoing Study with Weekly Administration of ALN-AAT

ALN-AAT in Transgenic Mice

Results
• Durable, dose dependent, sustained silencing
• Similar levels of knockdown in serum and mRNA
• Cumulative knockdown seen after repeat dose administration
  • SD 1mg/kg: 60% KD; Q1W x 3: >90% KD
ALN-AAT in Non Human Primates (NHP) Single Dose Data

- Exploring dose response, dosing regimens, and repeat dosing

- Single 1mg/kg dose leads to 60% KD
- Nadir after single dose is between day 20-30
- $ED_{50}$ NHP $\sim 0.6$mg/kg
- Serum AAT levels return to baseline on day 75
ALN-AAT in Non Human Primates (NHP) Pre-Clinical Results

- 1mg/kg q1w x12 and 3mg/kg q1m show similar knock-down
- AAT levels maintained for ~50 days post last dose Last dose administered

Last dose administered
Nonclinical Safety and Metabolism

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<td><strong>GLP-Compliant Safety Studies</strong></td>
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|                                                        | General Toxicology studies in rat and NHP  
• 13 week studies + 8 week recovery  
• Toxicokinetics and CNS evaluation (NHP) | Rat NOAEL ≥ 50 mg/kg  
NHP NOAEL ≥ 150 mg/kg |
| **Absorption, Distribution, Metabolism, Excretion (ADME) Studies** | PK/PD in rat, NHP  
Toxicokinetics for all Tox studies (plasma, liver, kidney)  
Metabolic profiling in rat, NHP (plasma, liver)  
Plasma protein binding (mouse, rat, NHP, human)  
In vitro CYP studies |

Safety margins of >160x (rat) and >500x (NHP), based on respective NOAELs and mg/kg translation
ALN-AAT Phase 1/2 Study
Dose-Escalation Study Including PiZZZ Patients

Study Design
- Randomized, single-blind, placebo-controlled SAD study in healthy volunteers (up to N=24)

Primary Objective
- Safety and tolerability of single dose in healthy volunteers

Secondary Objectives
- PK/PD and clinical activity
  - AAT levels in serum

Study Design
- Randomized, single-blind, placebo-controlled MAD study in healthy volunteers (up to N=24)

Primary Objective
- Safety and tolerability of multi-dose in healthy volunteers

Secondary Objectives
- PK/PD and clinical activity
  - AAT levels in serum

Study Design
- Randomized, single-blind MD study in PiZZZ patients (up to N=18)

Primary Objective
- Safety and tolerability of multi-dose in PiZZZ patients

Secondary Objectives
- PK/PD and clinical activity
  - AAT levels in serum
  - Z-AAT levels in liver

Initiated Phase 1 study, currently dosing healthy volunteers
ALN-AAT Clinical Development Plan

ALN-AAT for Alpha-1 Liver Disease

Phase 1/2

Adult Healthy Volunteers and PiZZ Patients

Key Objectives:
• Safety, PK and Clinical Activity (↓AAT in serum)
• Initial Dose Finding
• ↓ Z-AAT in liver in patients

Phase 2/3

Pediatric PiZZ Patients with Liver Disease

Key Objectives:
• Safety
• Clinical benefit (disease reversal or prevention)

OLE (Adult PiZZ Patients)

Key Objectives:
• Safety, PK and Clin Activity (↓AAT in serum) in chronic dosing
• Reversal of fibrosis liver in patients

Adult PiZZ Patients with Liver Disease (Fibrosis Stage 2-4)

Key Objectives:
• Safety
• Clinical benefit (improved liver histopathology)

Pediatric Natural History Studies (Retrospective Chart Review etc)

Adult Natural History Studies (NDA)
ALN-AAT Summary

ALN-AAT has potential to be promising investigational RNAi therapeutic for alpha-1 liver disease

• Significant unmet need for new therapeutic option for alpha-1 liver disease

• In pre-clinical studies, ALN-AAT showed potent, dose-dependent, and durable silencing of liver AAT mRNA and knockdown of serum AAT
  ◦ Efficacy with subcutaneous dose administration
  ◦ Chronic dosing leads to potent, dose-dependent and durable Z-AAT knock-down
  ◦ Efficient and robust Z-AAT knockdown in fibrotic livers
  ◦ Disease-modifying effects in Tg-PiZ mouse model
    – Reduction in Z-AAT globules
    – Reduced liver tumor burden
  ◦ Monthly dosing in NHP leads to ~90% reduction in serum AAT
    – Maximal levels of knock-down maintained for ~ 50 days after last dose
    – GLP safety and toxicology studies confirm wide therapeutic index

• Filed CTA and initiated Phase 1/2 study

• Clinical development plan in both adult and pediatric populations
Upcoming ALN-AAT Events

**Upcoming presentations**
- Initial clinical results expected in early 2016

**Upcoming planned milestones**
- To be updated in early 2016
Agenda

Welcome
• Joshua Brodsky
  Senior Manager, Investor Relations and Corporate Communications

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

Overview of AAT Deficiency-Associated Liver Disease
• Jeffrey Teckman, M.D., Professor of Pediatrics and Biochemistry, St. Louis University School of Medicine

Q&A Session
• With Dr. Teckman

ALN-AAT Program
• Al fica Sehgal, Ph.D.
  Principal Scientist, Research

Q&A Session
Upcoming RNAi Roundtables

Patisiran and Revusiran for the treatment of Transthyretin (TTR)-Mediated Amyloidosis
Thursday, August 20, 9:00 – 10:30 a.m. ET
• Eric Green, Vice President, General Manager, TTR Program
• Jared Gollob, M.D., Vice President, Clinical Research
• Moderator: Barry Greene, President and Chief Operating Officer
• Guest Speaker: Philip Hawkins, Ph.D., FRCPath, FRCP, FMedSci, Head, National Amyloidosis Centre, and Head, Periodic Fever Syndrome Service/Honorary consultant physician
• Guest Speaker: Isabelle Lousada, President & CEO, Amyloidosis Research Consortium, and Chairman, Amyloidosis Foundation

ALN-GO1 for the treatment of Primary Hyperoxaluria Type 1 (PH1)
Tuesday, September 8, 9:00 – 10:00 a.m. ET
• David Erbe, Ph.D., Director, Research
• Moderator: Barry Greene, President and Chief Operating Officer
• Guest Speaker: Sally-Anne Hulton, M.D., FRCPCH, MRCP, FCP, MBBCh, Consultant Paediatric Nephrologist and Clinical Lead, Birmingham Children’s Hospital NHS Trust

ALN-PCSsc for the treatment of Hypercholesterolemia
Wednesday, September 16, 9:30 – 10:30 a.m. ET
• Kevin Fitzgerald, Ph.D., Vice President, Research
• David Kallend, MBBS, Vice President and Global Medical Director, The Medicines Company
• Moderator: Barry Greene, President and Chief Operating Officer
• Guest Speaker: Marc S. Sabatine, M.D., M.P.H., Chairman, Thrombolysis in Myocardial Infarction (TIMI) Study Group at Brigham and Women’s Hospital, Lewis Dexter, MD Distinguished Chair in Cardiovascular Medicine, and Professor of Medicine, Harvard Medical School

ALN-AS1 for the treatment of Acute Hepatic Porphyrias
Tuesday, September 24, 11:00 a.m. – 12:00 p.m. ET
• Bill Querbes, Ph.D., Associate Director, Research
• Moderator: John Maraganore, Ph.D., Chief Executive Officer
• Guest Speaker: Robert J. Desnick, M.D., Ph.D., Dean for Genetics and Genomic Medicine, Professor and Chair Emeritus, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai Hospital

Replays, presentations, transcripts of all RNAi Roundtables available at www.alnylam.com/capella
Speaker Biographies

Akshay Vaishnaw, M.D., Ph.D.
Executive VP of R&D, and Chief Medical Officer, Alnylam

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. Akshay is a member of the Scientific Advisory Board of Scholar Rock, and a member of the Board of Directors for Visterra, Inc. In addition, he has published papers in leading scientific journals and authored a number of textbook chapters relating to autoimmune disease.

Jeffrey Teckman, M.D.
Professor, Department of Pediatrics, St. Louis University School of Medicine

Dr. Teckman is a pediatric gastroenterologist and Professor of Pediatrics and Biochemistry at the Saint Louis University School of Medicine in Saint Louis, Missouri. He has studied the cellular mechanisms of liver injury in alpha-1-antitrypsin deficiency for more than 20 years and participated in clinical studies and numerous patient education conferences. He received his medical degree from Washington University School of Medicine in St. Louis and trained in pediatrics and pediatric gastroenterology at Washington University and St Louis Children's Hospital. He is Director of Pediatric Gastroenterology and Associate Chair for Research at Cardinal Glennon Children's Hospital.

Alfica Sehgal, Ph.D.
Principal Scientist, Research, Alnylam

Dr. Sehgal joined Alnylam in 2008, coming from postdoctoral fellowships in cell biology at Johns Hopkins University School of Medicine and in infectious disease at Yale University. Alfica received her Ph.D. in molecular biology from the Tata Institute of Fundamental Research, India and her M.S. in plant molecular biology at the University of Delhi, India.
Thank You

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