ALN-AT3, an Investigational RNAi Therapeutic for the Treatment of Hemophilia and Rare Bleeding Disorders (RBD)

July 22, 2015
Agenda

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

Introduction
• John Maraganore, Ph.D.
  Chief Executive Officer

Overview of Hemophilia
• Margaret Ragni, M.D., MPH, Professor of Medicine, Division Hematology/Oncology, University of Pittsburgh, and Director, Hemophilia Center of Western Pennsylvania

Patient Perspectives
• Mark W. Skinner, J.D., Past President, World Federation of Hemophilia/National Hemophilia Foundation

Q&A Session
• with Dr. Ragni and Mr. Skinner

ALN-AT3 Program
• Benny Sorensen, M.D., Ph.D., Senior Director, Clinical Development

Q&A Session
Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches, 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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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
| GENETIC MEDICINES | | | | |
|------------------|-----------------|----------------|---------------|
| TTR-Mediated Amyloidosis | | | ALN-AT3 |
| Hemophilia and Rare Bleeding Disorders | | | |
| Complement-Mediated Diseases | | ALN-CC5 | |
| Hepatic Porphyrias | ALN-AS1 | | |
| Alpha-1 Antitrypsin Deficiency | | ALN-AAT | |
| Primary Hyperoxaluria Type 1 | ALN-GO1 | | |
| Beta-Thalassemia/Iron-Overload Disorders | ALN-TMP | | |
| Additional Genetic Medicine Programs | | | |

| CARDIO-METABOLIC DISEASES | | | |
|--------------------------|-----------------|----------------|
| Hypercholesterolemia | | ALN-PCSsc |
| Hypertriglyceridemia | ALN-AC3 | |
| Mixed Hyperlipidemia/Hypertriglyceridemia | ALN-ANG | |
| Hypertension/Preeclampsia | ALN-AGT | |
| Additional Cardio-Metabolic Programs | | |

| HEPATIC INFECTIOUS DISEASES | | | |
|-----------------------------|-----------------|----------------|
| Hepatitis B Virus Infection | ALN-HBV | |
| Hepatitis D Virus Infection | ALN-HDV | |
| Chronic Liver Infection | ALN-PDL | |
| Additional Hepatic ID Programs | | | |

**Alnylam Development Pipeline**

- Patisiran (ALN-TTR02)
- Revusiran (ALN-TTRsc)
- ALN-AT3
- ALN-CC5
- ALN-AS1
- ALN-AAT
- ALN-GO1
- ALN-TMP
- ALN-PCSsc
- ALN-HBV
- ALN-HDV
- ALN-PDL
# Alnylam Development Pipeline

<table>
<thead>
<tr>
<th>GENETIC MEDICINES</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
Hemophilia Update
07/22/15
Margaret V. Ragni, MD, MPH
<table>
<thead>
<tr>
<th>Event</th>
<th>Year</th>
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<tr>
<td>First case hemophilia in U.S.</td>
<td>1803</td>
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<tr>
<td>First whole blood transfusion</td>
<td>1840</td>
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<tr>
<td>Queen Victoria – son hemophilia - royalty</td>
<td>1843</td>
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<tr>
<td>Deficiency of factor VIII, IX</td>
<td>1930s</td>
</tr>
<tr>
<td>Plasma</td>
<td>1936</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>1964</td>
</tr>
<tr>
<td>Clotting factor: VIII, IX, PCC, FEIBA</td>
<td>1960s, 70s, 80s</td>
</tr>
<tr>
<td>Liver transplant: cure</td>
<td>1985</td>
</tr>
<tr>
<td>FIX, FVIII genes cloned</td>
<td>1982, 1984</td>
</tr>
<tr>
<td>Long-acting Factor IX, Factor VIII</td>
<td>2009, 2010</td>
</tr>
</tbody>
</table>
## Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
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<tbody>
<tr>
<td><strong>Genetics</strong></td>
<td>Xq28</td>
<td>Xq27</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>99% males</td>
<td>99% males</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>1/5000 males births</td>
<td>1/50,000 male births</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>20.6/10,000 males</td>
<td>5.3/10,000 males</td>
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<td><strong>Age</strong></td>
<td>Lifespan normal</td>
<td>Lifespan normal</td>
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<tr>
<td><strong>Race</strong></td>
<td>White 71.7%</td>
<td>69.6%</td>
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<tr>
<td></td>
<td>AA 12.6%</td>
<td>17.2%</td>
</tr>
<tr>
<td></td>
<td>Hisp 7.8%</td>
<td>4.7%</td>
</tr>
<tr>
<td></td>
<td>Other 7.9%</td>
<td>8.4%</td>
</tr>
</tbody>
</table>
THE COAGULATION SYSTEM

INTRINSIC SYSTEM

Surface Contact

XII → XIIa

XI → XIa

IX → IXa

Ca++

PF-3

VIII

X → Xa

PF-3

Ca++

V

II → IIa (Thrombin)

XIII → XIIIa

EXTRINSIC SYSTEM

Tissue Factor

VII → VIIa

PF-3

Ca++

I → Ia (Fibrin)
Clinical Presentation

Hemorrhage:
- Joints - Hemarthroses
- Muscles - Hematomas
- Infancy - Circumcision bleeding

Types: - 85% A, 15% B

Severity:
- Severe - Spontaneous & traumatic bleeds
- Moderate - Traumatic bleeds
- Mild - Rare traumatic bleeds

Treatment
- Standard - Costly, invasive, immunogenic
- Novel - Inhibit the inhibitors, EHL proteins
Hemarthrosis: Pathology

- Recurrent bleeding in joint
- Inflammatory response
- Inflammation reduces TF-VIIa activation
- Persistent bleeding into joint cavity
- Iron deposition, hemosiderin in joint
- Chondrocyte apoptosis
- Model: RA & DJD, but occurs in children
- Research study: will prophylaxis prevent joint damage?
Hemophilia Treatment

Early, accurate diagnosis, family history
Spontaneous mutation – 30%

Early, adequate factor replacement for bleeding
Reactive, invasive, costly, unavailable worldwide

Prophylaxis to prevent joint disease
Compliance erratic, < 50% adults do prophylaxis

Inhibitor formation major complication
Associated with early, high-dose Rx, high morbidity
Complications

1. Joint disease

2. Inhibitor formation

3. Transmissible agents: HCV-HIV co-infection

4. Co-existent coagulopathy
### 1. Prophylaxis

**RCT in hemo A<30 months (N=65): Landmark Trial - NEJM 2007**

Does prophylaxis prevent joint disease?

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>Standard therapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. joint damage (MRI)</strong></td>
<td>25 (93%)</td>
<td>16 (55%)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>No joint damage (Xray)</strong></td>
<td>27 (96%)</td>
<td>22 (81%)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>No. joint bleeds (no/pt/yr)</strong></td>
<td>0.20</td>
<td>4.35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Inhibitor formation</strong></td>
<td>2 (6.2%)</td>
<td>0 (0%)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Life-threatening bleeds</strong></td>
<td>0 (0%)</td>
<td>3 (9.1%)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>CVAD infections</strong></td>
<td>29 (91%)</td>
<td>25 (76%)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

**Conclusion:** Prophylaxis prevents joint damage and bleeds
Prophylaxis recommendations

Begin early with first bleed
Joint disease, pain, disability prevention
Compliance, frequency, invasiveness, cost

Problems with prophylaxis:

It is invasive, requiring 2-3 IV infusions per week
It prevents joint bleeds, damage, but <50% use it
2. Inhibitor Formation

Clinical: Leading complication of hemophilia
Hemorrhage unresponsive to FVIII
Risks: early high dose Rx, race, genetics

Defect: Prolonged APTT and APTT mix
Anti-VIII detection by Bethesda assay

Treatment: 1. Eradicate inhibitor (effective in ~70%)
   Immune Tolerance: F.VIII 75-200 U/kg/d

   2. Stop bleeding (suboptimal)
      FEIBA 50-75 U/kg q 8-12h (< 200 U/kg/day)
      rFVIIa 90 mcg/kg q 2-3h

Morbidity: 2x cost, 10x hospitalizations, 1.7-fold death
Inhibitor Prevention

28% develop inhibitors after 20-30 exposure days

Adapted, from Gouw, Blood 2013

I. Avoid “danger”

Inhibitors more common with early high intensity factor, surgery

II. Prolong half-life, promote tolerance

Gene Rx prevents inhibitors in hemA dog
EHL weekly prevents in hemA mice
EHL activate Tregs, reduces inhibitors in hem A

Give weekly EHL, before bleeds occur
3. HCV, HIV Infection in Hemophilia

HCV infection in 90% transfused 1970s, 1980s
- Exposure early in life, with first transfusion
- Now at 25+ yr HCV, 50% have grade ≥ 2 fibrosis

HIV infection in 80% (1978-1985), peak 1982
- 10+yr after HCV, HBV infection
- Of HCV(+), 40% have HIV-HCV co-infection
- Of HIV(+),  97% have HIV/HCV co-infection

HCV leading cause of death
4. Confounders of Hemostasis

1. Type of hemophilia
2. Co-existent thrombophilia
3. Co-existent hemostatic disorder
4. Thrombocytopenia
Treatment: What’s New?
## Standard Treatment

<table>
<thead>
<tr>
<th></th>
<th>Factor VIII</th>
<th>Factor IX</th>
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</thead>
<tbody>
<tr>
<td><strong>Goal:</strong></td>
<td>Treat, prevent bleeds</td>
<td></td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>FVIII 50 U/kg</td>
<td>FIX 75-100 U/kg</td>
</tr>
<tr>
<td><strong>Half-life:</strong></td>
<td>t½  8-12 hr</td>
<td>t½  12-24 hr</td>
</tr>
<tr>
<td><strong>Frequency:</strong></td>
<td>2-3 times weekly</td>
<td>1-2 times weekly</td>
</tr>
<tr>
<td><strong>Monitoring:</strong></td>
<td>F.VIII:C, APTT (trough)</td>
<td>F.IX:C, APTT (trough)</td>
</tr>
<tr>
<td></td>
<td>Anti-F.VIII</td>
<td>Anti-F.IX</td>
</tr>
<tr>
<td><strong>Inhibitors:</strong></td>
<td>FEIBA 50-75 U/kg q6-8 h</td>
<td>FIX to achieve &gt;0.50 U/ml</td>
</tr>
<tr>
<td></td>
<td>rFVIIa  90-180 mcg/kg q3h</td>
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</tbody>
</table>
Extended Half-Life Proteins

Fc fusion, Albumin-fusion, Pegylated Factor VIII, IX Proteins

1. Use same dose as recombinant factor
2. Decrease frequency based on half-life

75-100 U/kg BIW rFIX ~ 75-100 U/kg 1/Wk Aprolix

Children: Consider once-weekly dosing
Novel Pro-Hemostatic Agents

Inhibitors of Coagulation Inhibitors

ATIII: Anti-AT siRNA (ALN-AT3)
TFPI: Anti-TFPI

Mutated Coagulation Proteins

FX: Zymogen-FXa
FV: Super FVa
FVIII: PACE-furin cleaved FVIII bispecific VIII antibody

Versteeg, 2013
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Q&A Session
Living with Hemophilia – Today’s Reality

Mark W. Skinner, JD
Alnylam
22 July 2015
Hemophilia in the U.S. 1960’s

“The hemophiliac cannot live unless his blood is induced to clot by the addition of normal blood (or blood plasma).

...and now there is fresh frozen blood plasma which can be stored to provide a constant life-saving supply.”
"The Lonesomest Disease"

The author has to carry a physician's certificate in her handbag, to prove to strange doctors that she's really a "bleeder" and not a neurotic female.

Here's what is now being done for her and thousands of others who suffer from an ailment that can turn a minor cut into a major tragedy.

Dear Mrs. Sears:

The address of the National Hemophilia Foundation is:
175 Fifth Ave., New York, N.Y.

The address of the California Hospital Orthopedic Clinic:
115 S. Grand St., Los Angeles, Calif.

With our best wishes for your grandson's recovery,
we remain

Sincerely yours,

Eugene Anderson
Editorial Research

Mrs. R. H. Sears

February 19, 1960.
Development of Care in the United States

- 1950s
  - NHF Founded (1958)
- 1960s
  - Limited Treatment (whole blood, FFP)
  - Cryoprecipitate
  - WFH Founded (1963)
- 1970s
  - Factor concentrates
  - Home treatment
  - National care program
  - Treatment center network
- 1980s
  - HIV and HCV crisis
  - Viral inactivation
- 1990s
  - Recombinant established as standard of care
  - Prophylaxis
  - Immune tolerance
- 2000s
  - Quest for a cure
  - Improved efficacy
- 2010s
  - Health care reform
  - Advanced / Novel therapies
  - Personalized care
Past or Future Reality?
Global Disparity in Diagnosis

- Only 9% of patients identified with a bleeding disorder worldwide are from countries with a GNI per capita of <$1,500 USD.

- This group of countries represents one-third of the world’s population.

Source: WFH Global Survey 2010
Global Disparity in FVIII Consumption

75% of treatment products are consumed by 15% of the world’s population.

Source: P. Robert, Market Research Bureau 2012
Integrated “Comprehensive” Care

Hematologist
Physical Therapists
Nurses
Dentists
Social Workers
Laboratory Technicians
Orthopedists
Affordable Treatment – Access to Care

The 90:10 Challenge

Treatment Product Cost – Cost for All the Rest
Cell Phones & Landlines

- What will be the future evolution of treatment?
  - Health care infrastructure
  - Point of access to care

- Will developing countries benefit from the technology advances?
  - Long-lasting products
  - Gene transfer
  - Novel Therapies

Source: High & Skinner. Molecular Therapy 2011
Have we achieved normal?

• Does the current treatment approach allow for a fully “normal” life?

• There are many dimensions to defining normal
  - Burden of treatment
  - Factor levels / bleeding frequency
  - Lifespan
  - Work / Career
  - Family / Social life
  - Function / Mobility
  - Activity / Sport

• What are the outcomes important to patients to achieve normal?
Hemophilia Today – What it can be
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Q&A Session
Antithrombin (AT) is genetically defined target

- AT is key natural anticoagulant
  - Inactivates Factor Xa and thrombin
  - Attenuates thrombin generation
- Human AT deficiency associated with increased thrombin generation
- Expressed in liver; circulates in plasma

Co-inheritance of thrombophilic traits in hemophilia\(^1\)

- Associated with milder bleeding, reduced factor requirements, fewer complications
- Includes heterozygous
  - Antithrombin deficiency
  - Factor V Leiden
  - Protein C deficiency
  - Protein S deficiency

ALN-AT3 in clinical development

- Extensive pre-clinical efficacy and safety data in hemophilia models\(^2\)
- Orphan drug status in U.S./EU (HA/HB)
- Positive interim Phase 1 results
- Additional data expected late ’15

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\(^2\)Seghal et al., Nat Med, doi:10.1038/nm.3847
ALN-AT3 Pre-Clinical Efficacy

Potent AT Knockdown and Normalization of Thrombin Generation

- Weekly SC doses for >5 months result in potent, dose-dependent, and durable AT knockdown
- In NHP hemophilia “inhibitor” model, ALN-AT3 normalizes thrombin generation

Potent AT Knockdown and Normalization of Thrombin Generation in non-human primates (NHP)

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<table>
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<tr>
<th>Treatment</th>
<th>AT Knockdown (Pre-dose = 1)</th>
<th>Day</th>
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<td>0.5 mg/kg qw x 8</td>
<td>0.125 mg/kg qw x 12</td>
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<tr>
<td>1 mg/kg q2w x 4</td>
<td>Recovery</td>
<td></td>
</tr>
<tr>
<td>1.5 mg/kg qw x 5</td>
<td>Recovery</td>
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</tbody>
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<table>
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<tr>
<th>ALN-AT3 (mg/kg) qw</th>
<th>Relative Thrombin Generation†</th>
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</thead>
<tbody>
<tr>
<td>Pre-dose</td>
<td>~60% AT KD</td>
</tr>
<tr>
<td>Saline</td>
<td>~80% AT KD</td>
</tr>
<tr>
<td>0.25</td>
<td>~80% AT KD (Induced)</td>
</tr>
<tr>
<td>0.5</td>
<td>~80% AT KD (Induced)</td>
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```

†similar results obtained by ETP (p<0.01 at 0.50 mg/kg)
ALN-AT3 Pre-Clinical Efficacy
Potent AT Knockdown and Normalization of Thrombin Generation

Potent AT knockdown and normalized thrombin generation in non-human primates (NHP)

- Weekly SC doses for >5 months result in potent, dose-dependent AT knockdown.
- In NHP hemophilia “inhibitor” model, ALN-AT3 normalizes thrombin generation.

![Graph showing relative thrombin generation and AT knockdown over time](image)

**Recovery**
- 0.25 mg/kg qw x 12
- 1 mg/kg q2w x 4
- 1.5 mg/kg qw x 5

**Relative Thrombin Generation**
- Normal
- Hemophilia A (Induced)

**AT Knockdown**
- Pre-dose
- ALN-AT3 (mg/kg) qw

**Similar results obtained by ETP (p<0.01 at 0.50 mg/kg)**

Akinc, ISTH, July 2013
ALN-AT3 Phase 1 Study
Dose-Escalation Study in Three Parts

Primary objectives
• Safety, tolerability

Secondary objectives
• AT knockdown, thrombin generation

Part A: Single-Ascending Dose (SAD) | Randomized 3:1, Single-blind, Placebo-controlled, Healthy volunteers
30 mcg/kg x 1 SC, N=4

Part B: Multiple-Ascending Dose (MAD) – Weekly dosing | Open-label, Hemophilia A or B
15 mcg/kg qW x 3 SC, N=3
45 mcg/kg qW x 3 SC, N=6
75 mcg/kg qW x 3 SC, N=3

Part C: Multiple-Ascending Dose (MAD) – Monthly dosing | Open-label, Hemophilia A or B
225 mcg/kg qM x 3 SC, N=3

Presented January 2015
Up to 3 additional cohorts
## ALN-AT3 Phase 1 Study Part B (MAD)*
### Demographics & Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (N=3) 15 mcg/kg</th>
<th>Cohort 2 &amp; 3 (N=6) 45 mcg/kg</th>
<th>Cohort 4 (N=3) 75 mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>27 (9)</td>
<td>42 (14)</td>
<td>39 (4)</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>2</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Historical Annualized Bleed Rate (ABR)**, mean (SD)</td>
<td>18 (19.1)</td>
<td>16.3 (10.6)</td>
<td>6 (3.5)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>76 (10.1)</td>
<td>80 (21.5)</td>
<td>82 (8.5)</td>
</tr>
</tbody>
</table>

*Data as of 2 June 2015

** Calculated as the reported number of bleeding events in past 6 months multiplied by 2

Sorensen, ISTH, June 2015
ALN-AT3 Phase 1 Study Part B (MAD)*
Safety/Tolerability; All TEAEs

- No serious adverse events or discontinuations
- No thromboembolic events or clinically significant D-dimer increases
- Normal physical exams, vital signs, and ECG
- No clinically significant changes in any laboratory parameter (LFTs, CBC, coagulation)
- Majority of adverse events were bleed events
  - All bleed events successfully managed with replacement factor administration
  - No adverse events associated with factor administration
- A total of 17 single non-bleed adverse events were observed, all mild/moderate and transient

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (N=3) 15 mcg/kg</th>
<th>Cohort 2 &amp; 3 (N=6) 45 mcg/kg</th>
<th>Cohort 4 (N=3) 75 mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 TEAE</td>
<td>2 (67%)</td>
<td>4 (67%)</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>Total AEs</td>
<td>5</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

List of AEs
- Abdominal pain
  - Arthralgia
  - Costochondritis
  - Dyspepsia
  - Thermal burn
- Blood glucose increased
- Blood uric acid increased
- C-reactive protein increased
- Fall
- Injection site pain**
- Muscle tightness
- Nasopharyngitis
- Rhinitis
- Urticaria
- Arthritis
- Headache**
- Respiratory tract infection

*Data as of 2 June 2015: Adverse event grouping based on verbatim terms, excluding bleed events.
**Possibly related/Related
*Mild pain lasting 2 minutes, resolved, no other associated symptoms
Sorensen, ISTH, June 2015
ALN-AT3 Phase 1 Study Part B (MAD)**

AT Knockdown after multi-dose in hemophilia patients

<table>
<thead>
<tr>
<th>Cohort</th>
<th>AT Knockdown (Max ± SEM)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29 ± 12%</td>
<td></td>
</tr>
<tr>
<td>2&amp;3</td>
<td>54 ± 9%*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>4</td>
<td>59 ± 7%*</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05, relative to baseline

**Data as of 2 June 2015
Sorensen, ISTH, June 2015
ALN-AT3 Phase 1 Study Parts A and B**
Thrombin Generation

Post hoc analysis of thrombin generation by AT knockdown tertiles

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**Data as of 2 June 2015
Sorensen, ISTH, June 2015

<table>
<thead>
<tr>
<th></th>
<th>AT KD &lt;33%</th>
<th>AT KD 33-66%</th>
<th>AT KD &gt;66%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Volunteers</td>
<td>18 ± 8</td>
<td>35 ± 24</td>
<td>120 ± 81*</td>
</tr>
<tr>
<td>Severe Hemophilia</td>
<td>69 ± 92%</td>
<td>350 ± 239%*</td>
<td></td>
</tr>
</tbody>
</table>

% Increase in Peak Thrombin Generation (Mean ± SD)

*<p < 0.05, compared with AT knockdown less than 33%
Whole Blood Clot Formation
Materials and Methods

ROTEM® Thromboelastometry

- Evaluates viscoelastic changes in blood following physiologic coagulation stimulus
- CTI stabilized citrate whole blood; diluted tissue factor (Innovin®); CaCl₂

Hemophilia characterized by defect in propagation of whole blood clot formation; measured by Clot Formation Time (CFT)
### Whole Blood Clot Formation Results in All 3 Patients with ROTEM Data

**Improvement of whole blood clot formation; shortening of clot formation time**

- Day 1 mean CFT was $1166 \pm 614$ sec; Day 35 mean CFT was $323 \pm 46$ sec (p <0.05)

<table>
<thead>
<tr>
<th></th>
<th>101-009 45 mcg/kg</th>
<th>101-013 75 mcg/kg</th>
<th>101-016 75 mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AT KD (%)</strong></td>
<td>Representative Trace</td>
<td>CFT (sec) ± SEM</td>
<td>AT KD (%)</td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td>1</td>
<td>1441 ± 394</td>
<td>14</td>
</tr>
<tr>
<td><strong>Day 8</strong></td>
<td>30</td>
<td>625 ± 43</td>
<td>8</td>
</tr>
<tr>
<td><strong>Day 21</strong></td>
<td>57</td>
<td>289 ± 5</td>
<td>41</td>
</tr>
<tr>
<td><strong>Day 35</strong></td>
<td>56</td>
<td>333 ± 64</td>
<td>46</td>
</tr>
</tbody>
</table>

*AT KD (%) relative to baseline*  
*Sorensen, ISTH, June 2015*
Exploratory Analysis of Bleed Events*
Annualized Bleed Rate (ABR)

Post hoc analysis of bleed events by AT knockdown tertiles

<table>
<thead>
<tr>
<th></th>
<th>AT KD &lt;33%</th>
<th>AT KD 33-66%</th>
<th>AT KD &gt;66%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>12</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Cumulative Days</td>
<td>509</td>
<td>414</td>
<td>106</td>
</tr>
<tr>
<td>Cumulative Bleeds</td>
<td>33</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>ABR##, Mean (SEM)</td>
<td>22 ± 5</td>
<td>14 ± 5</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data as of 2 June 2015
#Number of patients with time spent in tertile
## For each patient, the ABR in each tertile is calculated by 365.24*(number of bleed events/number of days in tertile).
**Based on negative binomial regression model
Sorensen, ISTH, June 2015

**p<0.001
Hemophilia Patient 400-002*

Bleed-free period of 114 days correlates with AT KD and increase in thrombin generation, with no increase in D-dimer

*Patient 400-002 has severe hemophilia A and has a self-reported ABR of 22; enrolled in 45 mcg/kg dose cohort Sorensen, ISTH, June 2015
ALN-AT3 Product Opportunity

Significant potential for new therapeutic approach in hemophilia and rare bleeding disorders

• Differentiated approach with SC dosing that could change disease management by rebalancing hemostasis
• Potential to eliminate risk of inhibitor formation
• Potential to address all patient segments, including inhibitors
• Value supported by pharmacoeconomics
• Well organized patient advocacy
• Significant opportunity for global expansion
Current Market Needs

HA and HB Needs

- **Longer Duration**: Frequency of infusion (prophylaxis up to 3x’s / week) and potential for treatment with longer duration
- **Route of Administration**: IV is burdensome due to set-up and administration time, and pain associated with ‘poking’ the vein
- **Device**: Mixing devices, and vial / diluent sizes that make administration of IV factor products easier

Inhibitor Needs

- **Burden of Treatment**: very high burden – particularly in ITT which requires daily infusions and in prophylaxis therapy
- **Cost**: "Cost is an enormous burden" to system due to high volumes and frequent infusions demanded in inhibitor management
- **NovoSeven®**: Half-life too short
- **FEIBA**: Viscosity requires long mixing and infusion times

“Infusion is the biggest problem for me as I find it difficult to hit the vein in my first attempt.”

– Person with Hemophilia
Potential Target Bleeding Disorder Segments

- Total Population
- ALN-AT3 Initial Opportunity

<table>
<thead>
<tr>
<th>Category</th>
<th>Total Population</th>
<th>ALN-AT3 Initial Opportunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bleeding Disorders</td>
<td>309,265</td>
<td>30,138</td>
</tr>
<tr>
<td>Other Bleeding Disorders</td>
<td>~5,000</td>
<td></td>
</tr>
<tr>
<td>Addressable, Severe RBDs</td>
<td>69,169</td>
<td>~3,500</td>
</tr>
<tr>
<td>VWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 3 VWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild Hemophilia</td>
<td>70,878</td>
<td>6,583</td>
</tr>
<tr>
<td>Mod/Severe HA/HB Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod/Severe HA/HB Non-Inhibitors</td>
<td>123,999</td>
<td></td>
</tr>
</tbody>
</table>

Number of Patients

Adapted from WFH Annual Global Survey 2013, extrapolated to 2015
Clinical Development Plan
ALN-AT3 for the Treatment of Hemophilia and RBD

Broad-based development plan to maximize product opportunity

**Phase 1**
- Adult Healthy Volunteers and Hemophilia A/B
  - Key Objectives
    - Safety, PK, clinical activity (AT knockdown, thrombin generation)
    - Initial dose finding

**Phase 1 OLE**
- Hemophilia A/B
  - Key Objectives
    - Safety, PK, clinical activity (AT knockdown, thrombin generation, bleeding frequency)
    - Extended dosing

**Phase 3**
- On-demand (Non-Inhibitor)
- Inhibitor
  - Phase 3 Open Label Extension/Safety Non-inhibitor/Inhibitor
- RBDs
  - Pediatric (< 12 y.o.) ± Inhibitor

OLE: Open Label Extension
Summary

**ALN-AT3 is promising approach for treatment of hemophilia and rare bleeding disorders (RBD)**

- ALN-AT3 represents novel investigational approach for potential treatment of hemophilia and RBD
  - Potential to rebalance hemostasis to normalize thrombin generation
- In ongoing Phase 1 study in healthy volunteers (n=3) and patients with hemophilia (n=12), single- and multi-dose administration of ALN-AT3 generally well tolerated
  - Data cutoff date of June 2, 2015
  - No SAEs; all AEs mild or moderate, and transient; no discontinuations
  - No clinically significant increases in D-dimer
- Initial evidence for clinical activity and rebalancing of hemostasis in severe hemophilia
  - Up to 86% AT knockdown, with mean maximum AT knockdown of 59 ± 7% at 75 mcg/kg
  - Durable knockdown supportive of a once-monthly subcutaneous dose regimen
  - Increase of 350% in mean thrombin generation in highest AT knockdown tertile
    - Represents normalization of thrombin generation in severe hemophilia patients
  - Marked improvement in whole blood clot formation with over 3-fold shortening of clot formation time
    - No bleeds in highest AT knockdown tertile
    - Patient with highest degree of AT knockdown remained bleed-free for 114 days
Summary (continued)

**ALN-AT3 is promising approach for treatment of hemophilia and rare bleeding disorders (RBD)**

- Plan to advance to pivotal study in mid-2016
  - Additional Phase 1 clinical results expected to be presented in late-2015
  - Phase 1 OLE study expected to be initiated in late-2015

- Hemophilia and RBD represent attractive commercial opportunity
  - Applicability across broad segments of bleeding disorders with potential to address significant unmet needs

- Broad-based development plan to maximize product opportunity
Upcoming ALN-AT3 Events

Upcoming presentations
• 57th Annual Meeting of the American Society of Hematology (ASH)
  ◦ Pending abstract acceptance
  ◦ December 5-8, Orlando, FL

Upcoming milestones
• Present additional Phase 1 clinical results (late 2015); likely at ASH
• Initiate Phase 1 OLE study (late 2015)
• Initiate Phase 3 study (mid-2016)
Agenda

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

Introduction
• John Maraganore, Ph.D.
  Chief Executive Officer

Overview of Hemophilia
• Margaret Ragni, M.D., MPH, Professor of Medicine, Division Hematology/Oncology, University of Pittsburgh, and Director, Hemophilia Center of Western Pennsylvania

Patient Perspectives
• Mark W. Skinner, J.D., Past President, World Federation of Hemophilia/National Hemophilia Foundation

Q&A Session
• with Dr. Ragni and Mr. Skinner

ALN-AT3 Program
• Benny Sorensen, M.D., Ph.D., Senior Director, Clinical Development

Q&A Session
Upcoming RNAi Roundtables

**ALN-CC5 for the treatment of Complement-Mediated Diseases**
*Thursday, July 23, 9:00 – 10:00 a.m. ET*
- Pushkal Garg, M.D., Senior Vice President, Clinical Development
- Moderator: John Maraganore, Ph.D., Chief Executive Officer
- Guest Speaker: Regis Peffault de Latour, M.D., Ph.D, Professor, Hematology and Transplantation, Saint-Louis Hospital, Paris

**ALN-HBV for the treatment of Hepatitis B Virus (HBV) Infection**
*Tuesday, July 28, 4:00 – 5:00 p.m. ET*
- Laura Sepp-Lorenzino, Ph.D., Vice President, Entrepreneur-in-Residence
- Moderator: John Maraganore, Ph.D., Chief Executive Officer
- Guest Speaker: Edward Gane, MBChB, M.D., FRACP, MNZM, Professor of Medicine, University of Auckland (NZ), and Chief Hepatologist, Transplant Physician, Deputy Director of New Zealand Liver Transplant Unit, Auckland City Hospital

**ALN-AAT for the treatment of AAT Deficiency-associated liver disease**
*Friday, August 14, 2:00 – 3:00 p.m. ET*
- Alfica Sehgal, Ph.D., Principal Scientist, Research
- Moderator: Akshay Vaishnaw, M.D., Ph.D., Executive Vice President of R&D, Chief Medical Officer
- Guest Speaker: Jeffrey Teckman, M.D., Professor, Department of Pediatrics, St. Louis University School of Medicine

**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., FRCP, FRCPath, FMedSci, Head, National Amyloidosis Centre, and Head, Periodic Fever Syndrome Service/Honorary consultant physician

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

John Maraganore, Ph.D.
Chief Executive Officer, Alnylam

Since 2002, John Maraganore has served as the CEO and a Director of Alnylam. Prior to Alnylam he served as an officer and a member of the management team for Millennium Pharmaceuticals, Inc. As Senior Vice President, Strategic Product Development for Millennium, he was responsible for the company’s product franchises in oncology, cardiovascular, inflammatory, and metabolic diseases. He was previously Vice President, Strategic Planning and M&A and prior to that he was General Manager of Millennium BioTherapeutics, Inc., a former subsidiary of Millennium. Before Millennium he served as Director of Molecular Biology and Director of Market and Business Development at Biogen, Inc. At Biogen, Dr. Maraganore invented and led the discovery and development of Angiomax™ (bivalirudin for injection, formerly Hirulog™) currently marketed by The Medicines Company. Prior to Biogen, Dr. Maraganore was a scientist at ZymoGenetics, Inc., and the Upjohn Company. Dr. Maraganore received his M.S. and Ph.D. in biochemistry and molecular biology at the University of Chicago. Dr. Maraganore is a Director for Agios Pharmaceuticals and bluebird bio. He also serves as a Venture Partner with Third Rock Ventures. Dr. Maraganore is a member of the Biotechnology Industry Organization (BIO) Board and the BIO Executive Committee, and serves as the chair of the Emerging Company Section and as co-chair of the Regulatory Environment Committee.

Margaret V. Ragni, M.D., MPH
Professor of Medicine, Division Hematology/Oncology, Director, Hemophilia Center of Western PA

Dr. Ragni is Professor of Medicine and Clinical Translational Science, Division Hematology/Oncology and Director, Hemophilia Center of Western PA. She has been funded continuously from NIH for over 30 years and is currently PI of 4 NHLBI-funded studies, including a U34 Hemophilia Prophylaxis Study, a U34 Inhibitor Study, a U34 von Willebrand disease menorrhagia study, and a T35 student summer research training grant. She also collaborates on an NHLBI genotype-phenotype von Willebrand study; and past NIAID-funded organ transplant study in HIV, an NHLBI-funded hemophilia gene transfer, and an NHLBI-funded Transfusion Medicine/Hemostasis clinical trials network. She is a member of the Medical and Scientific Advisory Board, National Hemophilia Foundation and of the NHLBI Hemostasis & Thrombosis study section. She chaired the Hemophilia/VWD Subcommittee of the NHLBI State of the Science Symposium 2009, developing four clinical trial concepts, three submitted. She is a member of the ASH Development Committee, Contributing Editor to The Hematologist, and on the Editorial Board of Haemophilia. She was nominated to FDA Blood Products Advisory Committee and serves as Co-chair, Hemostasis Thrombosis Research Society Research Committee. Dr. Ragni is also Medical Director, Hemophilia Center of Western Pennsylvania, a position she has held since 1988. In this professional capacity Dr. Ragni is responsible for the care and treatment of hemophilia patients as well as the management and operation of the Center. She is also involved in teaching medical students, residents, and fellows.
Speaker Biographies

Mark W. Skinner, J.D.
President/CEO of the Institute for Policy Advancement, Ltd., Past President, World Federation of Hemophilia/National Hemophilia Foundation

Mark Skinner is President/CEO of the Institute for Policy Advancement, Ltd., a global health strategies consulting company, and a Senior Consultant to the Workers Compensation Research Institute. He has led both national and international patient organizations, including the World Federation of Hemophilia and National Hemophilia Foundation, where he currently serves on the Medical and Scientific Advisory Council. He is a board member of the American Thrombosis and Hemostasis Network, Blood Counts LLC, and BloodSource, and has held numerous roles as an advisor on critical blood safety and supply matters. Previously, he was Vice President of State Programs with the American Insurance Association and Administrative Assistant/Chief of Staff to the Speaker of the Kansas House of Representatives. He received degrees in Public and Business Administration from Kansas State University and a JD from Washburn University School of Law.

Benny Sorensen, M.D., Ph.D.
Senior Director, Clinical Development, Alnylam

Dr. Sorensen joined Alnylam in 2013 with more than 15 years of experience in clinical and academic hemophilia and hemostasis research and management. Before joining Alnylam, Dr. Sorensen was a Global Medical Director at Baxter Healthcare Corporation, where he was responsible for developing clinical, regulatory, commercial, and business development strategies for hemophilia products and services. Prior to Baxter he was the Director of the Haemostasis Research Unit and Honorary Lecturer at Guy's and St. Thomas’ Hospital & King’s College London School of Medicine, where he led the advancement of several clinical trials across Phases I, II, and III. Dr. Sorensen has published extensively on the topics of hemophilia and hemostasis management.
Thank You

www.alnylam.com