Fitusiran
Investigational RNAi Therapeutic for the Treatment of Hemophilia and Rare Bleeding Disorders

Monday, August 22, 2016
Agenda

Welcome
• Josh Brodsky, Associate Director, Investor Relations & Corporate Communications

Introduction
• Akin Akinc, Ph.D., Vice President, General Manager, Fitusiran

Overview of Hemophilia and Patient Perspective
• Brian O’Mahony, Chief Executive, Irish Haemophilia Society Ltd. and person living with severe hemophilia B

Fitusiran Program
• Akin Akinc, Ph.D., Vice President, General Manager, Fitusiran
• Benny Sorensen, M.D., Ph.D., Senior Director, Clinical Research

Q&A Session
Reminders

Event will run for approximately 75 minutes

Q&A Session at end of 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 and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; 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
RNAi Therapeutics
New Class of Innovative Medicines

Harness natural pathway

Catalytic mechanism

Silence any gene in genome

Upstream of today’s medicines

Clinically proven approach
Alnylam Strategic Therapeutic Areas (STArs)

Investigational pipeline focused in 3 STArs

Genetic Medicines
RNAi therapeutics for rare diseases

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

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

## GENETIC MEDICINES

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<thead>
<tr>
<th>Condition</th>
<th>Discovery</th>
<th>Development</th>
<th>Phase 1</th>
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## HEPATIC INFECTIOUS DISEASES

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*Updated August 9, 2016*
# Alnylam Development Pipeline

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Q&A Session
Haemophilia and Rare Bleeding Disorders

Brian O’Mahony
Chief Executive, Irish Haemophilia Society Ltd.
and person living with severe hemophilia B
Haemophilia A

- FVIII deficiency
- 105 per million males
- 1.05 per 10,000 males
- 80% of Haemophilia
Haemophilia B

- FIX Deficiency
- 28 per million males
- 0.28 per 10,000 males
- 20% of Haemophilia
Inheritance of Haemophilia

Sex linked Inheritance
– X chromosome

Carrier mother
– Sons 50% chance, haemophilia
– Daughters 50% chance, carriers

Man with Haemophilia
– Sons, no haemophilia
– Daughters, obligatory carriers

– 30% Spontaneous Mutation
Haemophilia - Severity

• Severe < 1%

• Moderate 1 to 5 %

• Mild 5 to 40%

• Severe - spontaneous bleeds
Von Willebrands

- Type 1
- Type 2A
- Type 2B
- Type 2N
- Type 3

0.1% of Population
Von Willebrands

- Chromosome 12
  - Affects males, females
  - Females often more symptomatic

<table>
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<tr>
<th>Severity</th>
<th>Proportion</th>
<th>Treatment</th>
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<tr>
<td>Type 1</td>
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<tr>
<td>Type 2</td>
<td>Moderate</td>
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<tr>
<td>Type 3</td>
<td>Severe</td>
<td>1:500,000</td>
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</table>
Bleeding

- Aura
- Pain, Heat, Swelling
- Damage

- Early treatment essential
• Haemarthrosis: 70-80%

• Muscle/soft tissue: 10-20%

• Other major bleeds: 5-10%

• Central nervous system bleeds: <5%
Incidence of bleeding into joints

- Knee 45%
- Elbow 30%
- Ankle 15%
- Shoulder 3%
- Wrist 3%
- Hip 2%
- Other 2%

• Target Joints
Treatment Principles

- Prevention of bleeding should be the goal
- Treat acute bleeds early
- Home therapy – early treatment
- Severe bleeds – hospital
- Avoid aspirin, Intramuscular injections, non steroidal anti inflammatory agents
- On demand treatment when bleeding occurs
- Prophylaxis- prevents spontaneous bleeds- maintain Factor level >1% at all times
Development of Replacement Therapy

• 1960’s: Plasma, Cryoprecipitate
• 1970’s: Plasma derived clotting Factor concentrates (CFCs)
• 1985-88: Virally inactivated plasma derived CFCs
• 1994: Recombinant CFCs
• 2014: Extended half life CFCs
Self-infusion Video
Current Treatment Options

• Cryoprecipitate, Plasma - only in absence of factor concentrates as an option
• Plasma derived factor concentrates – FVIII, FIX, VWD and rare bleeding disorders
• Recombinant Factor concentrates – FVIII, FIX and FXIII
• DDAVP- mild haemophilia
• Extended half life factor concentrates- FVIII, FIX
Personal Patient Journey
EHC Strategic objectives 2014-2017

1. Support and empower NMOs
2. Promote access to optimal treatment and comprehensive care for people with Haemophilia, VWD and RBDs
3. Ensure constructive engagement with key stakeholders
4. Increase influence on European policy-making environment
5. Ensure good governance and sustainability
NMO support

• NMO & multi-stakeholder workshops
  – Economics and HTAs
  – New Technologies
  – Tenders and Procurement
  – Youth Development

• European Inhibitor Program

• Annual Leadership conference

• EU Policy Reports for NMOs, 4 x year

• Annual Scientific conference
Treatment and care

• Collect and publish data annually
  – 2015: Haemophilia care in Europe (37 countries)
  – 2014: Tenders and procurement systems in Europe (37 countries)
  – 2016: Hepatitis C and Haemophilia

• Certification of EHCCCs/EHTCs

• Medical Advisory Group- statements on important issues

• Significant input into drafting of Council of Europe recommendations on haemophilia
### EHC data Collection and Publication

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<th>Region</th>
<th>Data Collection</th>
<th>Data Publication</th>
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<td>Sweden</td>
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**Haemophilia**

The Official Journal of the World Federation of Haemophilia, European Association for Haemophilia and Allied Disorders and the Hemostasis & Thrombosis Research Society

*Haemophilia (2015), 1–8*

**ORIGINAL ARTICLE**

Survey of coagulation factor concentrates tender and procurement procedures in 38 European Countries

B. O’Mahony, **+** D. Noone **+** and L. Prihodova **+**

*European Haemophilia Consortium, Brussels, Belgium; **+** Irish Haemophilia Society; **+** Trinity College, Dublin, Ireland; and **+** School of Psychology, University College, Dublin, Ireland*

Brian O Mahony, 2015
FVIII use per capita vs GDP 2014 data

FVIII consumption in IU/capita in Europe (in 2014) compared to national GDP (in USD)

3 IU/capita

Respondent countries

- FVIII IU/capita (2014)
- GDP 2014

Brian O Mahony, Unpublished data
Changes in FVIII use between 2008 and 2014

Changes in FVIII IU/Capita use 2008-2014

Countries reporting since 2008

[Bar chart showing changes in FVIII use between 2008 and 2014 for various countries.]

Brian O Mahony, Unpublished data
Stakeholders, Policymaking Environment

• Round Tables of Stakeholders
  – European Parliament hosted
  – 2016: Inhibitors, HCV, Ageing, Outcome Measures

• Representation
  – EMA
  – COMP
  – European Commission Expert Group for Rare Diseases
  – European Parliament MEP Group
  – Council of Europe and EDQM

• Comprehensive newsletters, 3 x year
• World Haemophilia Day events
The Future when I was Born: *Peanuts for haemophilia*

**ANIMAL PHYSIOLOGY**

A Peanut Factor for Hæmostasis in Hæmophilia

It is known that there are unpredictable apparent remissions of clinical symptoms enjoyed by hæmophiliacs; but these remissions have not been correlated with any influences such as time of year, food eaten, weather conditions, other diseases, or physical condition of the patient. The lack of...

Boudreaux HB & Frampton VL
Nature 185: 469-470 (1960)
What People with Haemophilia want?

• To avoid or prevent bleeds and micro bleeds
• To treat bleeds effectively and with minimum disruption when they occur
• To be able to lead a normal life and engage in normal activities
• Treatment that is safe and effective
• Treatment that is convenient and easy to administer
What People with Haemophilia want?

• Oral treatment – not currently feasible
• Subcutaneous treatment
• Less frequent intravenous infusion – EHL CFCs
• Treatment that lasts longer and gives higher factor levels or more protection
• Treatment designed with patients in mind as end users - not clinicians or nurses
• To go from a severe form of hemophilia (<1-2%) to a mild form (>5%)
• Possibility of a cure - Gene therapy
Ideal Treatment Options

• Non intravenous treatment
• Safe and effective
• Better treatment options for inhibitors
• More treatment options for VWD and RBDs
• Treatment that minimizes disruption of life
• Economically sustainable to allow access to treatments by payers
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Q&A Session
Hemophilia and Rare Bleeding Disorders (RBD) Unmet Need

- Hemophilies are recessive X-linked monogenic bleeding disorders
  - Hemophilia A: deficiency in Factor VIII (~160,000 diagnosed pts WW)
  - Hemophilia B: deficiency in Factor IX (~40,000 diagnosed pts WW)
- Debilitating disease characterized by repeated bleeding into musculoskeletal system
- Very high treatment burden for prophylactic therapy
  - Complications arise from repeated IV access
  - Real-world efficacy suboptimal due to reduced compliance
- Inhibitor patients\(^1\)\(^,\)\(^2\) represent a segment of very high unmet need
  - 2,000 Patients in major markets; up to 6,000 WW
  - >15-25 Bleeds/year; >5 in-hospital days/year
  - ~$300,000/year avg. cost; up to >$1M/year
- Other RBD with segments of unmet need
  - Inadequate prophylaxis options for RBD patients with severe bleeding phenotypes

\(^1\) WFH 2012 Global Survey; \(^2\) Antunes et al., Haemophilia. 20:65-72 (2014)
Hemophilia
Emerging Therapeutic Landscape

Exciting new approaches for the management of hemophilia are in development

• Modified Factor Replacement Therapies
  ◦ Physiochemical engineering of factor replacements to extend half-life and reduce immunogenicity

• Gene Therapy
  ◦ Single administration of gene vector with potential to lessen disease severity by eliciting continuous production of factor

• TFPI Inhibitors
  ◦ Agents blocking TFPI, an inhibitor of coagulation, as a way to promote coagulation

• Bispecific Antibodies
  ◦ Emicizumab (ACE910) is a bispecific IgG antibody that binds FIXa and FX, thus mimicking the function of FVIII cofactors and promoting thrombin generation

• RNA Interference Therapeutics
  ◦ Fitusiran is a siRNA targeting antithrombin in order to increase thrombin generation
Fitusiran
Investigational RNAi Therapeutic for Treatment of Hemophilia

**Fitusiran (ALN-AT3)**
- SC-administered small interfering RNA (siRNA) therapeutic targeting antithrombin (AT)
  - Non-biologic, chemically-synthesized, with targeting ligand to specifically deliver to liver—site of AT synthesis
  - Harnesses natural RNA interference (RNAi) mechanism for regulation of plasma AT levels

**Therapeutic hypothesis**
- Hemophilia A and B are characterized by ineffective clot formation due to insufficient thrombin generation
- Fitusiran is designed to lower AT, with goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding
  - Observation of ameliorated bleeding phenotype in patients with co-inheritance of thrombophilic traits in hemophilia\(^1\)-\(^4\)
  - Supported by pre-clinical data\(^5\) and emerging Phase 1 clinical results\(^6\)

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Fitusiran
A New Approach

Several emerging features for potential differentiation

• Not a biologic – it is a manufactured RNAi therapeutic
• No reconstitution or mixing required
• Administered subcutaneously (SC), as opposed to intravenously (IV)
• Long duration of action, currently being evaluated in Phase 1/2 studies, administered as once-monthly dose
• Not a factor, therefore may help avoid inhibitor formation due to reduced factor exposure and intensity
• Mechanism directed at addressing thrombin production defect, amenable to hemophilia A and hemophilia B, including those who have developed inhibitors – and potentially other RBD
• Stable at room temperature – no cold chain required
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Q&A Session
## Fitusiran Phase 1 Study

Dose-Escalation Study in Four Parts

### 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, Patients with 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: MAD – Monthly dosing | Open-label, Patients with Hemophilia A or B†

- **225 mcg/kg qM x 3 SC, N=3**
- **450 mcg/kg qM x 3 SC, N=3**
- **900 mcg/kg qM x 3 SC, N=3**
- **1800 mcg/kg qM x 3 SC, N=3**
- **80 mg qM x 3 SC, N=6**

### Part D: MAD – Monthly dosing | Open-label, Patients with Hemophilia A or B with inhibitors

- **50 mg qM x 3 SC, N=6**
- **80 mg qM x 3 SC, N=6**

Note: 5 patients participating in Part C previously participated in Part B.

qW, weekly; qM, monthly; SC, subcutaneous

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*Ongoing*
## Interim Fitusiran Phase 1 Study Results*

Demographics & Baseline Characteristics, Parts B, C & D

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<th>Part C Subcutaneous Monthly × 3</th>
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<td>6</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Weight (kg), mean (SD)</strong></td>
<td>76 (10)</td>
<td>80 (22)</td>
<td>82 (8)</td>
<td>85 (12)</td>
<td>76 (16)</td>
<td>76 (2)</td>
</tr>
</tbody>
</table>

Pasi et al., WFH, July 2016
Interim Fitusiran Phase 1 Study Results*
Safety/Tolerability†, Parts B, C, & D

- No SAEs related to study drug
- Majority of AEs mild or moderate in severity
  - AEs (excluding ISRs) in ≥10% of patients
    - Upper respiratory tract infection (10%), arthralgia (10%)
- 11 (35%) patients reported drug-related ISRs, all mild
  - Mostly pain and/or erythema at injection site
- One patient discontinued due to AE of non-cardiac chest pain; considered severe and possibly related
  - Associated with transient elevations of ALT (10x ULN), AST (8x ULN), CRP and D-dimer; no increase in total bilirubin
  - Extensive evaluation unremarkable; VTE excluded by serial CT angiograms and liver and lower extremity ultrasound
  - This event resolved with symptomatic management, including antacids and analgesics
- No thromboembolic events or laboratory evidence of pathologic clot formation (D-dimer, platelet count, fibrinogen, and/or PT/INR)
- With exception of case noted above, no other clinically significant drug-related changes in laboratory parameters
- No instances of anti-drug antibody (ADA) formation
- Bleed events successfully managed with infusion of standard replacement factor or bypass agents

*Data transfer up to 11 July 2016
Pasi et al., WFH, July 2016
†Adverse event grouping based on MedDRA-coded terms, excluding bleed events
Interim Fitusiran Phase 1 Study Results*
AT Lowering, Part C

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

% Mean (+/- SEM) AT Activity Relative to Baseline

Days since first dose

Onset Observation

Cohort 1 225 mcg/kg (N=3)
Cohort 2 450 mcg/kg (N=3)
Cohort 3 900 mcg/kg (N=3)
Cohort 4 1800 mcg/kg (N=3)
Cohort 5 80 mg (N=6)

*Data transfer: 30Jun2016
Pasi et al., WFH, July 2016
Interim Fitusiran Phase 1 Study Results*
AT Lowering, Parts A, B & C

Dose-dependent AT lowering

- Mean maximal AT lowering of 87 ± 1% at 80 mg fixed dose
Interim Fitusiran Phase 1 Study Results*
Thrombin Generation, Part B & C

Post hoc analysis of thrombin generation by AT lowering quartiles
- Mean thrombin generation increase of 289% relative to baseline at AT lowering >75% (p<0.001†)

Boxes denote median and interquartile range

*Data transfer: 30Jun2016; Pasi et al., WFH, July 2016
†%Change in Peak TG: p<0.001 by Mann-Whitney test, when compared with AT3 lowering than <25% group
Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Factor Equivalence

Fitusiran achieved peak thrombin generation values equivalent to >40% Factor VIII

- Pre-dose factor administration used to establish individualized factor-peak thrombin relationship (in all 3 patients with pre-dose factor data)
  - Plasma collected at -0.5, 1, 2, 8, 24, and 48 hours post factor administration
  - Samples analyzed for FVIII level and thrombin generation
- Peak thrombin achieved post fitusiran dose compared to peak thrombin achieved with >40% FVIII

C1-1 (225 mcg/kg qM)
C4-3 (1800 mcg/kg qM)
C5-6 (80 mg qM)

Pre-dose Factor
Peak Thrombin
AT % Lowering
Peak Thrombin

*Data transfer: 30Jun2016
Pasi et al., WFH, July 2016
Post hoc analysis of bleed events by AT lowering quartiles

- Includes more than 1100 cumulative days with AT lowering >75% in 16 patients

<table>
<thead>
<tr>
<th>AT Lowering</th>
<th>Patients†</th>
<th>Cumulative Days</th>
<th>Cumulative Bleeds</th>
<th>ABR‡, Mean (SEM)**</th>
<th>ABR, Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>30</td>
<td>733</td>
<td>47</td>
<td>22 ± 5</td>
<td>10</td>
</tr>
<tr>
<td>25-50%</td>
<td>27</td>
<td>1119</td>
<td>40</td>
<td>15 ± 6</td>
<td>0</td>
</tr>
<tr>
<td>50-75%</td>
<td>25</td>
<td>1203</td>
<td>36</td>
<td>11 ± 3</td>
<td>6</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>16</td>
<td>1128</td>
<td>11</td>
<td>5 ± 2</td>
<td>1</td>
</tr>
</tbody>
</table>

**P-value < 0.05

*ABR, annualized bleeding rate; SEM, standard error of the mean
†Number of patients with time spent in quartile; ‡For each patient, the ABR in each quartile is calculated by 365.24*(number of bleed events/number of days in quartile)

Data transfer: 30Jun2016; Pasi et al., WFH, July 2016
Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events

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

*Data transfer: 30Jun2016; Pasi et al., WFH, July 2016
Patient has severe hemophilia A and has a self-reported ABR of 22; enrolled in Part B (45 mcg/kg dose cohort)
Plot updated on 11Aug2016 to reflect corrected peak thrombin values (reruns conducted on samples with assay errors)
# Interim Fitusiran Phase 1 Study Results*

Exploratory Analysis of Bleed Events, Part C†

<table>
<thead>
<tr>
<th>Dose</th>
<th>Patient</th>
<th>Prior Tx</th>
<th>Pre-study ABR‡</th>
<th>Onset ABR</th>
<th>Observation Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All Bleeds, n</td>
</tr>
<tr>
<td><strong>225 mcg/kg</strong></td>
<td>C1-1</td>
<td>PPx</td>
<td>2</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>C1-2</td>
<td>PPx</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>C1-3</td>
<td>PPx</td>
<td>0</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td><strong>450 mcg/kg</strong></td>
<td>C2-1</td>
<td>PPx</td>
<td>4</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>C2-2</td>
<td>OD</td>
<td>38</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>C2-3</td>
<td>PPx</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>900 mcg/kg</strong></td>
<td>C3-1</td>
<td>PPx</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>C3-2</td>
<td>OD</td>
<td>20</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>C3-3</td>
<td>OD</td>
<td>32</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td><strong>1800 mcg/kg</strong></td>
<td>C4-1</td>
<td>PPx</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>C4-2</td>
<td>OD</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>C4-3</td>
<td>PPx</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td><strong>80 mg^</strong></td>
<td>C5-1</td>
<td>PPx</td>
<td>12</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>C5-2</td>
<td>PPx</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>C5-3</td>
<td>PPx</td>
<td>6</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>C5-5</td>
<td>PPx</td>
<td>6</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>C5-6</td>
<td>PPx</td>
<td>0</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data transfer: 30Jun2016; Pasi et al., WFH, July 2016

PPx: Prophylaxis, OD: On-Demand; ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate

†Post hoc analysis of treated bleed events during Onset (Day 0-28) and Observation periods (Day 29 to last study visit or last dose+56 days, whichever is earlier; ‡Pre-study ABR derived from medical records; ^Patient C5-4 withdrawn, excluded from analysis
Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events, Part C†

Summary of Median ABR (All Cohorts, n=17^)

Summary of Median ABR (80 mg, n=5)

All Part C patients^:
- Median ABR, Pre-study period: 2 (PPx); 28 (OD)
- Median ABR, Observation period: 0
  - 53% of patients report no bleeds
  - 82% of patients report no spontaneous bleeds

Part C, 80 mg dosing cohort^:
- Median ABR, Pre-Study (all PPx patients): 6
- Median ABR, Observation period: 0

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*Data transfer: 30Jun2016; Pasi et al., WFH, July 2016
PPx: Prophylaxis, OD: On-Demand; ABR, annualized bleeding rate;
†Post hoc analysis of treated bleed events during Onset (Day 0-28) and Observation periods (Day 29 to last study visit or last dose+56 days, whichever is earlier; ‡Pre-study ABR derived from medical records; ^Patient C5-4 withdrawn, excluded from analysis
Fitusiran Phase 1 Study
Inhibitor Patients, Part D

Study population
• Hemophilia A and Hemophilia B patients with inhibitors, utilizing bypassing agents (BPAs) for bleed management

Exploratory pre-dose evaluation of response to BPAs
• BPA administered prior to fitusiran dosing to explore peak thrombin response to patient’s standard BPA
  ◦ Plasma collected at -1, 2, 6, and 24 hours post BPA administration, and samples analyzed for thrombin generation

Fitusiran dose cohorts
• First cohort (N=6) enrolled and dosed at fixed, low monthly dose of 50 mg
• Second cohort (N=6) enrolled and being dosed at fixed, monthly dose of 80 mg
  ◦ Follow-up ongoing
Interim Fitusiran Phase 1 Study Results*
AT, Peak Thrombin, Part D (Cohort 1, 50 mg)

Initial AT lowering and thrombin generation results in patients with inhibitors
• Comparable AT lowering and thrombin generation as observed with similar doses in non-inhibitor patients
• Thrombin generation with fitusiran consistently exceeds transient levels achieved with BPA administration

*Data transfer: 11July2016
Pasi et al., WFH, July 2016
Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events, Part D (Cohort 1, 50 mg)†

<table>
<thead>
<tr>
<th>Dose</th>
<th>Patient</th>
<th>Hemophilia</th>
<th>Prior Tx</th>
<th>Prescribed BPA</th>
<th>Pre-study ABR‡</th>
<th>Onset ABR</th>
<th>Observation Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Days in Obs Period</td>
</tr>
<tr>
<td>50 mg</td>
<td>D1-1</td>
<td>HA w/ inh</td>
<td>OD</td>
<td>aPCC</td>
<td>40</td>
<td>13</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>D1-2</td>
<td>HB w/ inh</td>
<td>OD</td>
<td>rFVIIa/aPCC</td>
<td>26</td>
<td>13</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>D1-3</td>
<td>HA w/ inh</td>
<td>OD</td>
<td>rFVIIa</td>
<td>0</td>
<td>0</td>
<td>0**</td>
</tr>
<tr>
<td></td>
<td>D1-4</td>
<td>HA w/ inh</td>
<td>OD</td>
<td>aPCC</td>
<td>52</td>
<td>38</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>D1-5</td>
<td>HA w/ inh</td>
<td>OD</td>
<td>PCC</td>
<td>80</td>
<td>38</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>D1-6</td>
<td>HA w/ inh</td>
<td>OD</td>
<td>rFVIIa</td>
<td>16</td>
<td>13</td>
<td>57</td>
</tr>
</tbody>
</table>

- Data suggest partial effect at 50 mg (49-100% reduction in Pre-study ABR)
- Further follow-up ongoing to explore safety and bleed efficacy with longer-term dosing; all eligible patients (reaching Day 84) have rolled over to extension study
- Second cohort dosed at 80 mg; follow-up ongoing

*Data transfer: 11Jul2016
Pasi et al., WFH, July 2016
w/ inh, with inhibitors; PPx, Prophylaxis; OD, On-Demand; ABR, annualized bleeding rate
**As of data transfer date, patient does not have sufficient follow up in Observation period
†Post hoc analysis of treated bleed events during Onset (Day 0-28) and Observation periods (Day 29 to last study visit or last dose+56 days, whichever is earlier); ‡Pre-study ABR derived from medical records
Fitusiran Phase 1 Study*
Summary of Interim Results

Fitusiran generally well tolerated in hemophilia A and B patients with and without inhibitors

• No SAEs related to study drug; no thromboembolic events
• AEs (excluding ISRs) in ≥10% of patients: upper respiratory tract infection (10%) and arthralgia (10%); majority mild or moderate in severity
• 11 (35%) patients reported mild drug-related ISRs
  ◦ Mostly pain and/or erythema at the injection site
• 1 discontinuation due to AE; event resolved in this patient with symptomatic management

Evidence of clinical activity and potential correction of hemophilia phenotype in non-inhibitor patients

• Dose-dependent AT lowering and thrombin generation increase achieved, with once-monthly subcutaneous dose regimen; fixed 80 mg dose provides consistent AT lowering >75%
• In exploratory post-hoc analysis in monthly dose cohorts, fitusiran achieved median ABR = 0, with 53% patients bleed-free and 82% patients experiencing zero spontaneous bleeds

Encouraging early data in inhibitor patients

• AT lowering and thrombin generation increase consistent with non-inhibitor patients
  ◦ Thrombin generation increases consistently exceed those achieved transiently with BPA administration
• Exploratory post-hoc analysis shows 49-100% reduction of bleeds at initial 50 mg dose
• Second cohort (N=6) now fully enrolled at 80 mg

*Data transfer: up to 11Jul2016
Pasi et al., WFH, July 2016
Fitusiran Program
Next Steps

21 patients enrolled (as of July 11, 2016) in open-label extension (OLE) study, including inhibitor patients
• As of the July 11, 2016 data cutoff date, patients had received up to 13 monthly doses of fitusiran

Additional data expected to be shared in late 2016, likely at ASH, pending abstract approval
• Updated results from Parts C and D of the ongoing Phase 1 study
  ◦ Highest and fixed dose cohorts, including inhibitor patients
• Initial results from Phase 1/2 OLE study

Plan to advance to pivotal studies in early 2017
Preliminary Fitusiran Phase 3 Design*
Both studies expected to begin in early 2017

**STUDY 1†**
*Population:*
- Adults and adolescents with Severe Hemophilia A or B with inhibitors
- N~50

[2:1 RANDOMIZATION]

**Fitusiran**

**OR**

**SOC**

*Endpoints (at 9 months):*
- Annualized Bleed Rate
- Total number of bleeds
- By-passing agent consumption
- QoL
- Safety

**STUDY 2†**
*Population:*
- Adults and adolescents with Severe Hemophilia A or B with inhibitors
- N~100

[2:1 RANDOMIZATION]

**Fitusiran**

**OR**

**SOC**

*Endpoints (at 9 months):*
- Annualized Bleed Rate
- Total number of bleeds
- Factor VIII/IX consumption
- QoL
- Safety

*Preliminary plans subject to further diligence and health authority feedback
†Patients in both Study 1&2 will be allowed to roll over into open-label extension
Agenda

Welcome
• Josh Brodsky, Associate Director, Investor Relations & Corporate Communications

Introduction
• Akin Akinc, Ph.D., Vice President, General Manager, Fitusiran

Overview of Hemophilia and Patient Perspective
• Brian O’Mahony, Chief Executive, Irish Haemophilia Society Ltd. and person living with severe hemophilia B

Fitusiran Program
• Akin Akinc, Ph.D., Vice President, General Manager, Fitusiran
• Benny Sorensen, M.D., Ph.D., Senior Director, Clinical Research

Q&A Session
Upcoming RNAi Roundtables

ALN-CC5 for the treatment of Complement-Mediated Diseases
Wednesday, August 31, 11:00 a.m. – 12:00 p.m. ET
• Jeff Miller, Vice President, General Manager, CC5 Program
• Pushkal Garg, M.D., Senior Vice President, Clinical Development
• Guest Speaker: Anita Hill, M.D., Ph.D., MRCP, FRCP, Consultant Haematologist for Leeds Teaching Hospitals NHS Trust, UK, and Lead for the National PNH Service in England

ALN-AS1 for the treatment of Acute Hepatic Porphyrias
Tuesday, September 13, 11:30 a.m. – 12:45 p.m. ET
• John Maraganore, Ph.D., Chief Executive Officer
• William Querbes, Ph.D., Associate Director, Research
• Guest Speaker: Ariel Lager, living with Acute Intermittent Porphyria

ALN-GO1 for the treatment of Primary Hyperoxaluria Type 1 (PH1)
Tuesday, September 27, 10:00 a.m. – 11:00 a.m. ET
• Barry Greene, President and Chief Operating Officer
• David Erbe, Ph.D., Director, Research
• Guest Speaker: Sally-Anne Hulton, M.D., FRCPCH, MRCP, FCP, MBBCh, Consultant Paediatric Nephrologist and Clinical Lead, Birmingham Children’s Hospital NHS Trust
• Guest Speaker: Jennifer Lawrence, M.D. (mother of George Tidmore, a PH1 patient)

ALN-HBV for the treatment of Hepatitis B Virus (HBV) Infection
Tuesday, October 11, 9:00 a.m. – 10:00 a.m. ET
• Barry Greene, President and Chief Operating Officer
• Laura Sepp-Lorenzino, Ph.D., Vice President, Entrepreneur-in-Residence
• Guest Speaker: Heiner Wedemeyer, M.D., Managing Senior Physician and Assistant Professor in the Department of Gastroenterology, Hepatology and Endocrinology at Hannover Medical School

For more information, please visit www.alnylam.com/roundtables
2016 RNAi ROUNDTABLE

Thank you

www.alnylam.com