Hemophilia Overview
Guy Young, M.D.
A brief history of hemophilia
Talmud—2nd Century

“If she circumcised her first son and he died and a second one also died, she must not circumcise the third son”

R. Judah, the Patriarch, redactor of the Mishnah
Moses Maimonides was a physician and religious scholar who refined the teachings of the Talmud as follows:

“If a woman had her first son circumcised and he died as a result of the circumcision, which enfeebled his strength, and she similarly had her second [son] circumcised and he died as a result of the circumcision - whether [the latter child] was from her first husband or her second husband - the third son may not be circumcised at the proper time [on the eighth day of life]...”


He understood that hemophilia is X-linked.
Conrad Otto

- In 1803, the first clear description of hemophilia in the medical literature titled: “An Account of an Hemorrhagic Disposition Existing in Certain Families”
- He was able to trace the origin to a woman who settled in Plymouth, New Hampshire in 1720
First transfusion and lab test

- Samuel Lane was the first to treat hemophilia by giving a patient a blood transfusion in 1840.

- The first blood test for hemophilia was developed in 1893 demonstrating that blood did not clot normally in a capillary tube.

Physiologic Mechanism of Hemophilia
Thrombin’s procoagulant effects on coagulation

- Fibrinogen (I) → Fibrin
- Fibrinogen (I) → Thrombin (IIa)
- VIII → VIIIa
- XI → Xla
- V → VIIIa
- Va → VIIIa
- XIII → XIIIa
- TAFI → TAFIa

Thrombin (IIa)
Physiologic Coagulation

Prothrombin (II) → Thrombin (IIa) → Fibrinogen (I) → Fibrin → Cross-linked fibrin

V → Va

IX → IXa

VIII → VIIIa

VII → VIIa

X → Xa

Ca++

TF

CHLA.org/HTC
Natural Coagulation Inhibitors

- **Prothrombin (II)**
  - Inhibits (**---**) (Thrombin (IIa))

- **Fibrinogen (I)**
  - Fibrin
  - Cross-linked fibrin

- **VIII**
  - VIII (Ca++)
  - Thrombin (IIa)

- **IX**
  - IX (Ca++)
  - IXa
  - Thrombin (IIa)

- **FX**
  - FX (Ca++)
  - FXa
  - Thrombin (IIa)

- **Protein C**
  - Inhibits (Antithrombin)

- **Thrombin (IIa)**
  - Inhibits (Antithrombin)

- **Xa**
  - Inhibits (Protein S)

- **Protein S**
  - Inhibits (Protein C)

- **Cross-linked fibrin**

**Tissue factor pathway inhibitor (TFPI)**

**CHLA.org/HTC**
Coagulation in Hemophilia

VII
\[ \text{ TF } \]
VIIa
\[ \text{ Ca}^{++} \]
X
\[ \text{ Xa } \]
\[ \text{ Ca}^{++} \]
Prothrombin (II)
\[ \text{ Thrombin (IIa) } \]
The lack of thrombin generation is the cause of bleeding in hemophilia.
Clinical Presentation
Unusual Bruising
Joint Bleeding
Muscle Bleeding
Mucus Membrane Bleeding
Post-traumatic Bleeding
Internal Bleeding
How can we generate thrombin in patients with hemophilia?
Whole Blood

1900

Plasma

1950s

Cryoprecipitate

1960s

Plasma-derived intermediate purity concentrates

1970s

Plasma-derived high purity concentrates

1980s

Plasma-derived concentrates

1990s

Recombinant factors

2000s

First gene therapy trials

2010s

First extended half-life factors
Treatment Drawbacks

- Replacement of missing protein
  - Requires intravenous infusion
    - Leads to use of central venous catheters
  - Frequent infusions
    - High treatment burden
  - Antibody (inhibitor development)
    - These patients can no longer use replacement therapy
- Not curative
- Cost
How can these be overcome?

• Can we treat without replacing the missing protein?
  – Alternative administration routes (s.c.)
  – Less frequent administrations
  – Reduced/No immunogenicity
  – Treat patients with inhibitors

• If we have to treat with replacement therapy, can it be made less burdensome?

• Can we cure hemophilia with gene correction?
Novel treatments

1. Extended half-life factors
2. Rebalancing the coagulation system
   - Anti-Antithrombin siRNA
   - Anti-tissue factor pathway inhibitor
3. Factor VIII mimetics
   - Bispecific antibodies
4. Gene therapy
#1: Extended Half-life Factors

**Pros**

- Factor replacement
  - Proven
  - Easily understood
  - “Natural”
- Less frequent than standard factor concentrates

**Cons**

- Risk for inhibitors
- IV infusion
  - Still at least once every two weeks and for most patients twice weekly
- Inconvenience of storing a lot of boxes and ancillary supplies
#2: Rebalancing the Coagulation System: Natural Coagulation Inhibitors

- **Inhibits (-----→)**

**Tissue factor pathway inhibitor (TFPI)**

**Antithrombin**

**Prothrombin (II)**

**Thrombin (IIa)**

**Fibrinogen (I)**

**Fibrin**

**Cross-linked fibrin**
#2: Rebalancing the Coagulation System
No FVIII—Bleeding Disorder

FIX
FX
FII

TFPI
AT
PC
PS

Bleeding Disorder
No AT—Clotting Disorder

Diagram showing a balance with FVIII, FIX, FX, FII on one side and TFPI, PC, PS on the other side, indicating a clotting disorder without AT.
Absent FVIII and absent AT—
Rebalancing the Coagulation System
#2: Rebalancing the Coagulation System

Rebalancing agents

**Pros**

- Subcutaneous route of administration
- Long half-life
  - Infrequent injections
- No risk for antibody formation against clotting factors
- Effective in inhibitor patients
- Can be effective in all factor deficiency disorders

**Cons**

- Less intuitive than factor replacement
- Theoretical risk for thrombosis
- Laboratory monitoring
#3: Bispecific antibody
#3: Bispecific antibody

**Pros**
- Subcutaneous route of administration
- Long half-life so infrequent injections required
- Mimics FVIII activity so relatively easily understood
- Effective in inhibitor patients

**Cons**
- Only effective in hemophilia A
- Antibody formation
- Theoretical risk for thrombosis
- Laboratory monitoring
#4: Gene Therapy

**Pros**
- Potentially curative

**Cons**
- “Messing” with our DNA
- Current technology leading to immune reactions in most patients
- Achievable levels with current technology are not truly “curative”
Improving the care of hemophilia is a “tall order”
Fitusiran (ALN-AT3) for Hemophilia & Rare Bleeding Disorders

Benny Sorensen, M.D., Ph.D.
Senior Director, Clinical Research
Hemophilia and Rare Bleeding Disorders Program
Unmet Need and Product Opportunity

High unmet needs in hemophiliaia and rare bleeding disorders (RBD)

- Hemophiliaias are recessive X-linked monogenic bleeding disorders
  - Hemophilia A: loss of function in Factor VIII
    - >40,000 Patients in EU/U.S.
  - Hemophilia B: loss of function in Factor IX
    - ~9,500 Patients in EU/U.S.

- Segments of high unmet need remain
  - E.g., “Inhibitor” patients\(^1,2\)
    - 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

- Hemophilia A and B represent >$9B market
  - Premium pricing established
  - Value supported by pharmacoconomics
  - Well organized patient advocacy
  - Significant opportunity for global expansion

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

**Alnylam Reproducible and Modular Platform**

|   | **Genetically validated, liver-expressed target gene** | **Antithrombin** (AT) is key natural anticoagulant  
Co-inheritance of AT deficiency with hemophilia associated with milder bleeding phenotype |
|---|--------------------------------------------------|--------------------------------------------------------------------------------------------------|
| **1** | - Genetically validated, liver-expressed target gene | **Antithrombin** (AT) is key natural anticoagulant  
Co-inheritance of AT deficiency with hemophilia associated with milder bleeding phenotype |
| **2** | **Biomarker for POC in Phase 1** | **Biomarker for POC in Phase 1**  
Blood-based biomarkers measure components in coagulation cascade:  
- **AT**  
- **Thrombin Generation** |
| **3** | **Definable path to approval and market** | **Definable path to approval and market**  
Two separate pivotal trials in inhibitor and on-demand patients  
Established Endpoint: **Annualized Bleeding Rate** |
Fitusiran
Investigational RNAi Therapeutic for the 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 bleeding disorders 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
  - Supported by pre-clinical data and emerging Phase 1 clinical results

Fitusiran Phase 1 Study
Dose-Escalation Study in Three Parts

**Primary objectives**
- Safety, tolerability

**Secondary objectives**
- AT lowering, 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

Presented January 2015¹

**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

Presented June 2015²

**Part C: Multiple-Ascending Dose (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

Presented December 2015³

Ongoing

Up to 2 additional cohorts

¹Akinc A et al. Goring Coagulation Conference (2015)
Interim Fitusiran Phase 1 Study Results*
Demographics & Baseline Characteristics, Parts B & C

<table>
<thead>
<tr>
<th></th>
<th>Part B SC, Weekly × 3</th>
<th>Part C SC, Monthly × 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 mcg/kg</td>
<td>45 mcg/kg</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>27 (9)</td>
<td>42 (14)</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>76 (10.1)</td>
<td>80 (21.7)</td>
</tr>
</tbody>
</table>

*Data as of 12 November 2015
Interim Fitusiran Phase 1 Study Results*
Safety/Tolerability, Parts B & C†

• No SAEs related to study drug and no discontinuations
  ◦ One subject was hospitalized due to re-activation of hepatitis C, not drug related

• AEs reported
  ◦ Total of 35 AEs occurred in 14 patients
    – 33 single AEs + 2 AE episodes of arthritis
    – 34 Mild/Moderate, 1 Severe‡
  ◦ 3 drug related AEs were observed – all mild:
    – Injection site reactions:
      » One patient (45 mcg/kg) experienced mild transient pain
      » One patient (1800 mcg/kg) experienced mild transient erythema & pain
    – Other:
      » Headache, transient
  ◦ No thromboembolic events or clinically significant D-dimer increases
  ◦ No drug related clinically significant changes in physical exams, vital signs, ECG or laboratory parameter (LFTs, CBC, coagulation)
  ◦ Bleed events successfully managed with standard replacement factor administration

• No instances of anti-drug antibody (ADA) formation

†Adverse event grouping based on MedDRA-coded terms, excluding bleed events
‡Hypertriglyceridemia
Interim Fitusiran Phase 1 Study Results*
AT Lowering, Part B

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

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Mean Max AT Lowering ± SEM</th>
<th>Max AT Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mcg/kg (N=3)</td>
<td>29 ± 12%</td>
<td>53%</td>
</tr>
<tr>
<td>45 mcg/kg (N=6)</td>
<td>55 ± 9%</td>
<td>86%</td>
</tr>
<tr>
<td>75 mcg/kg (N=3)</td>
<td>61 ± 8%</td>
<td>74%</td>
</tr>
</tbody>
</table>

*Data as of 12 November 2015
Interim Fitusiran Phase 1 Study Results*
AT Lowering, Part C

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

*Data as of 12 November 2015
Interim Fitusiran Phase 1 Study Results*
AT Lowering, Parts A, B & C

Mean maximum AT lowering by monthly equivalent dose

#Single dose only (1 of 3)
Interim Fitusiran Phase 1 Study Results*
Thrombin Generation, Part B & C

Post hoc analysis of thrombin generation by AT lowering quartiles

<table>
<thead>
<tr>
<th>AT Lowering</th>
<th>Peak Thrombin Generation, nM (Mean ± SD)</th>
<th>% Increase in Peak Thrombin Generation (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>18 ± 9</td>
<td>20 ± 72%</td>
</tr>
<tr>
<td>25-50%</td>
<td>26 ± 12</td>
<td>48 ± 61%</td>
</tr>
<tr>
<td>50-75%</td>
<td>47 ± 29</td>
<td>218 ± 272%</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>62 ± 27**</td>
<td>285 ± 165%**</td>
</tr>
</tbody>
</table>

**p < 0.001, compared with AT lowering less than 25%

*Data as of 12 November 2015; reruns conducted of samples with analytical errors

Interim Fitusiran Phase 1 Study Results*
Thrombin Generation, Part B & C

Post hoc analysis of thrombin generation by AT lowering quartiles

<table>
<thead>
<tr>
<th>AT Lowering</th>
<th>N</th>
<th>Mean ± SD (Peak Thrombin Generation)</th>
<th>Mean ± SD (% Increase in Peak Thrombin Generation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25%</td>
<td>24</td>
<td>18 ± 9</td>
<td>20 ± 72%</td>
</tr>
<tr>
<td>25 - 50%</td>
<td>21</td>
<td>26 ± 12</td>
<td>48 ± 61%</td>
</tr>
<tr>
<td>50 - 75%</td>
<td>18</td>
<td>47 ± 29</td>
<td>218 ± 138%</td>
</tr>
<tr>
<td>&gt; 75%</td>
<td>9</td>
<td>62 ± 27**</td>
<td>285 ± 165%**</td>
</tr>
</tbody>
</table>

*Data as of 12 November 2015; reruns conducted of samples with analytical errors
Interim Fitusiran Phase 1 Study Results*

Exploratory Analysis of Factor Equivalence

- 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 FVIII

Achieved peak thrombin generation values equivalent to >40% factor VIII

Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events, Parts B & C

Post hoc analysis of bleed events by AT lowering quartiles

<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>24</td>
<td>602</td>
<td>43</td>
<td>34 ± 10</td>
<td>13</td>
</tr>
<tr>
<td>25-50%</td>
<td>21</td>
<td>838</td>
<td>34</td>
<td>20 ± 7</td>
<td>11</td>
</tr>
<tr>
<td>50-75%</td>
<td>18</td>
<td>862</td>
<td>35</td>
<td>14 ± 4</td>
<td>10</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>9</td>
<td>304</td>
<td>3</td>
<td>6 ± 3</td>
<td>0</td>
</tr>
</tbody>
</table>

†Number of patients with time spent in quartile
‡For each subject, the ABR in each quartile is calculated by 365.24*(number of bleed events/number of days in quartile).
**Based on negative binomial regression model

**p<0.05
Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events, Part C

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)

Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events, Part C†

Post hoc analysis of bleed events by individual and Part C median

- Available Median Part C (Cohorts 1-3) Observation Period ABR = 4.3 (85% reduction relative to median Historical On-Demand ABR)
- Median Cohort 2 & 3 Observation Period ABR = 2.2 (92% reduction relative to median Historical On-Demand ABR)

†Observation Period data for Cohort 4 (1800 mcg/kg) not yet available
#Historical On-Demand ABR value not available; excluded from summary median ABR calculation
ABR Results in Select Prospective Studies*
Median ABR ranges from 1.1 to 7.9

*The above graph does not reflect data from head-to-head studies and direct comparisons can not be made.
Potential Product Features*

<table>
<thead>
<tr>
<th></th>
<th>Fitusiran</th>
<th>ACE910</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence for Reduced ABR</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Potential Indications</td>
<td>Hem A, Hem B,</td>
<td>Hem A</td>
</tr>
<tr>
<td></td>
<td>potentially other RBDs</td>
<td></td>
</tr>
<tr>
<td>Administration &amp; Volume</td>
<td>S.C., &lt;1mL</td>
<td>S.C., &gt;1mL</td>
</tr>
<tr>
<td>Frequency</td>
<td>Once Monthly</td>
<td>Once Weekly</td>
</tr>
<tr>
<td>Development of ADA</td>
<td>None – 0%</td>
<td>3/18 patients$^1$ – 17%</td>
</tr>
<tr>
<td>Injection Site Reactions</td>
<td>2/24 patients – 8%</td>
<td>4/18 patients$^1$ – 22%</td>
</tr>
<tr>
<td>Storage Conditions</td>
<td>Room temperature</td>
<td>Refrigeration</td>
</tr>
</tbody>
</table>

*Analysis not based on comparative studies
$^1$Shima et al., WFH, May 2014
Significant potential for new therapeutic approach in hemophilia and rare bleeding disorders

- Differentiated approach with monthly, subcutaneous dosing that could change disease management by restoring hemostasis
- Potential to eliminate risk of inhibitor formation
- Potential to address hemophilia A and B, 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 Development**: Concern because of immense burdens of treatment and management

**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 Bleeding Disorders: 309,265
- Other Bleeding Disorders: 30,138
- Addressable, Severe RBDs: ~5,000
- VWD: 69,169
- Type 3 VWD: ~3,500
- Mild Hemophilia: 70,878
- Mod/Severe HA/HB Inhibitors: 6,583
- Mod/Severe HA/HB Non-Inhibitors: 123,999

Note: Numbers are adapted from WFH Annual Global Survey 2013, extrapolated to 2015.
# Fitusiran Target Product Profile
## Hemophilia A and B

<table>
<thead>
<tr>
<th>Fitusiran</th>
<th>Target Product Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>• Prevention of bleeding in patients with hemophilia A/B without or with inhibitors</td>
</tr>
<tr>
<td><strong>Dose and Regimen</strong></td>
<td>• ≤ 1 mg/kg monthly (qM)</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>• ≤ 1ml, subcutaneous injection via auto-injector</td>
</tr>
</tbody>
</table>
| **Efficacy**               | Primary • >75% reduction in all bleeding episodes  
|                            | Secondary • Reduction in annualized joint, spontaneous, & traumatic bleeding episodes  
|                            | • Reduction in factor usage  
|                            | • Improvement in Hem-QoL  
|                            | • Impact on joint structure (MRI) and function |
| **Safety**                 | • Very low incidence of mild-moderate ISRs  
|                            | • No significant impact on liver or kidney function |

Target product profiles for investigational RNAi therapeutics reflect current thinking on desired product characteristics and are subject to change.
Clinical Development Plan
Fitusiran 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**
  - N=24+/N=6 inhibitor, ETC late-2018
- **Key Objectives**
  - Safety, PK, clinical activity (AT knockdown, thrombin generation, bleeding frequency)
  - Extended dosing

**Phase 3**

- **Inhibitor N=45, ETC late 2017**
- **On-demand (Non-Inhibitor) N=100, ETC mid-2018**
- **Phase 3 Open Label Extension/Safety**
  - Non-inhibitor/Inhibitor N=TBD, ETC late 2020
- **RBDs**
  - Pediatric (< 12 y.o.) ± Inhibitor N=10/N=40, ETC late 2020

OLE: Open Label Extension
ETC: Estimated Time to Completion

Key Objectives:
- Safety, PK, clinical activity (AT knockdown, thrombin generation)
- Extended dosing

Pediatric (< 12 y.o.) ± Inhibitor

On-demand (Non-Inhibitor)
**Preliminary Fitusiran Phase 3 Design**

**STUDY 1†**

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

3:1 RANDOMIZATION

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

**STUDY 2†**

**Population:**
- Adults and adolescents with Severe Hemophilia A or B with inhibitors
- N~45

2:1 RANDOMIZATION

**Endpoints (at 9 months):**
- Annualized Bleed Rate
- Total number of bleeds
- By-passing agent 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
Fitusiran Program Summary & Next Steps

Fitusiran is promising investigational approach for treatment of hemophilia and rare bleeding disorders (RBD)

• Potential to address significant unmet need and could represent attractive commercial opportunity

Positive data from ongoing Phase 1 Study

• Generally well tolerated in hemophilia A and B patients with both weekly and monthly SC dose regimens (N=24)
• Clinical activity results support further advancement
  ◦ Up to 88% AT lowering achieved, with once-monthly subcutaneous dose regimen
  ◦ Clinically meaningful increases in thrombin generation
  ◦ 85-92% reduction in median estimated ABR

Next Steps

• Phase 1 OLE study initiated
• Additional Phase 1 clinical results expected in mid and late 2016
• Plan to advance to Phase 3 studies in mid 2016