A potential new approach to preventing bleeds
Changing how we think about hemophilia

- Hemophilia and other bleeding disorders are caused by the body’s inability to accomplish the natural clotting process.
- People with hemophilia experience bleeds because there is an inadequate amount of thrombin due to a deficiency of factor VIII or IX.

HEMOPHILIA SEVERITY IS RELATED TO THE ABILITY TO GENERATE THROMBIN

<table>
<thead>
<tr>
<th>Severity</th>
<th>Relative Thrombin Generation (%)</th>
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<tbody>
<tr>
<td>NO HEMOPHILIA</td>
<td>100%</td>
</tr>
<tr>
<td>MILD</td>
<td>44%</td>
</tr>
<tr>
<td>MODERATE</td>
<td>17%</td>
</tr>
<tr>
<td>SEVERE</td>
<td>8%</td>
</tr>
</tbody>
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People with lower levels of thrombin usually have more severe hemophilia symptoms.

Thrombin & clotting: a critical relationship

- Thrombin’s function in your body is to create fibrin, an essential component of the natural clotting process.
- But when factor VIII or IX is deficient, insufficient thrombin is produced to support natural clotting.
- The goal of hemophilia treatment is to prevent bleeds by improving thrombin levels.
  - Factor replacement therapy temporarily allows the body to produce enough thrombin to support clotting.

THROMBIN IS GENERATED TO AID IN BLOOD CLOTTING AFTER AN INJURY
People with hemophilia have very low levels of thrombin²

But because they have normal levels of antithrombin, the thrombin that's there is kept in check⁴

When thrombin is prevented from working, insufficient fibrin is made which results in an inability to clot⁴

Why do some people bleed less often?

- A prospective observational study looked at 72 people with severe hemophilia A and B⁵
  - All had factor VIII or IX levels <1%

- The goal of the study was to determine which blood proteins, besides factor, might influence the severity of hemophilia symptoms⁵

OF THE 72 PARTICIPANTS WITH SEVERE HEMOPHILIA, TWO PEOPLE WITH MILD SYMPTOMS HAD LOW LEVELS OF A BLOOD PROTEIN CALLED ANTITHROMBIN⁶

If we could decrease the amount of antithrombin in people with hemophilia, could we improve thrombin production and enable natural clotting?
### Treatment goal for hemophilia

**MAIN GOAL**

Protect against bleeds by improving thrombin levels sufficiently enough to prevent bleeds

<table>
<thead>
<tr>
<th><strong>TRADITIONAL THERAPIES</strong></th>
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<tr>
<td>Factor VIII or IX infusions may temporarily allow the body to produce enough thrombin to support clotting⁴</td>
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<tr>
<td>Recombinant factor VIIa and activated prothrombin complex concentrates can treat people with inhibitors who have very little factor VIII or IX activity¹</td>
</tr>
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</table>
Fitusiran (ALN-AT3): An investigational RNA interference (RNAi) therapeutic in development for the treatment of hemophilia\(^6,7\)

- Fitusiran targets antithrombin, with the goal of improving thrombin production
- Fitusiran is administered subcutaneously (SC)
- Fitusiran is not a biologic and is not gene therapy
- Alnylam is investigating fitusiran for the treatment of people with hemophilia A and hemophilia B, including those who have developed inhibitors
- Fitusiran is currently being evaluated in a Phase 2 study, with Phase 3 trials expected to begin in 2017
LEARN MORE ABOUT RNA INTERFERENCE (RNAi)

How is antithrombin (AT) produced?⁴,⁸,⁹

1. DNA
   - Antithrombin Gene
   - Your body’s DNA contains the instructions to make all proteins, including antithrombin.

2. RNA
   - Antithrombin Message
   - To create a specific protein like antithrombin, a piece of DNA (the antithrombin gene) is copied to make RNA. RNA is the messenger that carries the instructions to make antithrombin protein.

How does RNAi decrease antithrombin levels?

- RNAi targets the antithrombin message
- Antithrombin RNA is degraded
- Less antithrombin protein is made

- RNAi is a natural process that helps your body recognize specific RNA messages and degrade them, resulting in less protein made. Investigational RNAi therapies take advantage of this system to decrease the amount of specific targets, like antithrombin.

- Targeting and degrading antithrombin message with RNAi means less antithrombin is made.
RNAi: A new investigational approach to drug discovery and development

RNAi is a revolution in biology
RNAi is a natural mechanism of gene silencing that occurs in organisms ranging from plants to animals

Investigational RNAi Therapeutics
A potential new class of innovative medicines based on a 2006 Nobel Prize-winning discovery
Harness a natural pathway found in all humans for regulating protein production

Investigational RNAi Therapeutics Are Not
Gene therapy — no changes are made to the gene
Biologics — not produced from human plasma or animal cells

History of RNAi

1990 - First scientific report of RNAi phenomenon in which Napoli and Jorgensen report that violet petunias turned white instead of a deeper violet

1998 - Fire and Mello published a paper that reported a potent gene silencing effect in worms and coined the term RNA interference

2002 - Alnylam founded with a core focus on developing RNAi therapeutics

2006 - Fire and Mello awarded the 2006 Nobel Prize in Physiology or Medicine
Who are we?

• Alnylam was founded in 2002 to advance RNAi therapeutics as a potential new class of innovative medicines
• Our pipeline has a strong focus on rare diseases, with other areas of investigation that include cardio-metabolic and hepatic infectious diseases
• Our commitment to innovation and excellence is reflected in everything we do, earning us a globally recognized leadership position in the science of RNAi therapeutics

RNAi experts, dedicated to developing unique solutions

• Our priority is to bring new solutions to rare and difficult-to-treat conditions
• We’re dedicated to fulfilling unmet clinical needs with a broad pipeline of products based on our novel RNAi platform
• We’re committed not only to making a positive impact on human health, but to serving patient communities through education, empathy and awareness

Find out about new developments in our hemophilia program by signing up for Alnylam Patient Connect at Alnylam.com/connect-hemophilia
We know RNAi

As of January 2017, we’ve administered more than:

**14,000 doses** in our clinical trials using investigational RNAi therapeutics, based on a Nobel Prize-winning technology

8 clinical stage programs*

3 late stage programs*

References:
A POTENTIAL NEW THERAPEUTIC OPTION IN DEVELOPMENT FOR ALL TYPES OF HEMOPHILIA, REGARDLESS OF PRESENCE OF INHIBITORS

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