2016 RNAi Roundtable: Fitusiran for the Treatment of Hemophilia and Rare Bleeding Disorders Corporate Call

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PRESENTATION

Operator

Thank you, ladies and gentlemen, for joining today's RNAi Roundtable. We will be conducting a web-based question-and-answer session during the webcast. You may submit your question at any time during today's presentation by clicking the ask a question button located above the slide window in the webcast player.

I would now like to turn the call over to Josh Brodsky for opening remarks. Josh, you may proceed.

Josh Brodsky, Alnylam Pharmaceuticals, Inc. - Associate Director, IR & Corporate Communications

Thank you. Good morning everyone and thanks for joining us for the RNAi Roundtable to discuss the progress we are making with fitusiran in development for the treatment of hemophilia and rare bleeding disorders.

I am Josh Brodsky, Associate Director of Investor Relations and Corporate Communications at Alnylam. And with me today are Akin Akinc, Vice President, General Manager of the fitusiran program here at Alnylam; Brian O'Mahony of the Irish Haemophilia Society; and Benny Sorensen, Senior Director of Clinical Research at Alnylam.

I will be turning the call over to Akin shortly who will provide you with a brief introduction but first I'd like to make a few comments. Today's RNAi Roundtable focused on our fitusiran program is the second in a series of roundtables that we are hosting this summer and early fall. Today's event will run for about 75 minutes and will conclude around 11:45 a.m. Eastern. Akin will moderate a web-based Q&A session with our speakers at the conclusion of their presentations and you may submit a question at any time during the webcast by clicking on the ask a question button that's located above the slide window on the webcast player.

Finally, as a reminder we will be making forward-looking statements. And we encourage you to read our most recent SEC filings for a more complete discussion of risk factors.

And so with that I will turn the call over to Akin.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Thank you, Josh. I think we have a very interesting program and in particular I'm very grateful to have Brian O'Mahony join us to provide an overview and his very unique personal perspective on hemophilia.

As many of you know, since our founding in 2002 Alnylam has been singularly focused on bringing RNAi therapeutics, a new class of innovative medicines, to patients. RNAi therapeutics harnessed a natural endogenous pathway for gene regulation. Without altering the genes themselves RNAi therapeutics have the potential to silence or down-modulate the production of any protein coded by any gene in the genome and they do this in a reversible and dose-dependent manner.

Importantly, RNAi therapeutics have now demonstrated clinical proof-of-concept in multiple human clinical trials across multiple indications and disease settings. Alnylam's pipeline of investigational RNAi therapeutics is organized in three strategic therapeutic areas or STArs. These include genetic medicine representing mainly greater distances, cardio metabolic diseases and hepatic infectious disease.

Alnylam's development pipeline, organized by strategic therapeutic area, is shown on slide 8. As you can see, we now have 10 programs in active clinical testing, including two programs in hereditary ATTR amyloidosis in Phase 3 and we have demonstrated clinical proof-of-concept in all six of our most advanced programs. The focus of today's roundtable is on fitusiran, our genetic medicines program in the area of hemophilia and rare bleeding disorders.

Turning our attention back to the agenda, next we will hear from Brian on an overview of hemophilia and the patient perspective. We will then come back to fitusiran where I'll provide a very brief introduction before handing it over to Benny who will share the most recent clinical experience with fitusiran. We will then end with a Q&A session.

Throughout the presentation, as Josh mentioned, please remember to submit any questions you may have. You can do so by clicking the ask a question button located above the slide window on the webcast player.

So now I will turn it over to Brian.

Brian O'Mahony, Irish Haemophilia Society Ltd. - Chief Executive

Thank you, I'm on slide 11. So I'm going to speak about hemophilia and very briefly mention rare bleeding disorders.

Next slide please. The most common type of hemophilia is Factor VIII deficiency, and this occurs in 105 per million males or just over one in 10,000 males. And in most countries this constitutes about 80% of the hemophilia population.

Next slide. The second most common type of hemophilia is Factor IX deficiency. This, in fact, was the deficiency that Queen Victoria was a carrier of and the Czar's son in Russia had Factor IX deficiency. This occurs in about 28 per million males, about

0.28 per 10,000 males and it constitutes about 20% of the hemophilia population.

Next slide. The inheritance of hemophilia, it's sex linked on the X chromosome. So basically the defect is carried on the X chromosome, usually carried by the female and generally affects males.

A woman who is a carrier who, of course, she has two X chromosomes. So each of her sons has a 50% chance of having hemophilia and her daughters have a 50% chance of being carriers. A man with hemophilia, on the other hand, his sons will not have hemophilia, they will get his Y chromosome, but his daughters are always going to be obligatory carriers.

So you can see, therefore, I think quite clearly why the vast majority of the cases of severe hemophilia are in males and very rarely in females. About 30% of cases are spontaneous mutations with no previous family history.

Next slide. The severity of hemophilia, well, severe hemophilia is categorized in less than 1%, which means that you have less than 1% of the normal clotting factor activity in your blood. Moderate is 1% to 5% and mild is 5% to 40% or 5% to 50%. And in severe hemophilia you get spontaneous bleeds which have no traumatic cause.

Next slide. Von Willebrand's disease is more complex. You have type 1, type 2 and type 2 with type 2 being subdivided into three types. And this constitutes 0.1% of the population.

Next slide, slide 17. Von Willebrand's affects both of males and females and females are often more symptomatic due to menstruation and pregnancy. But 75% of the von Willebrand's cases are mild and they can be treated with synthetic hormone called DDAVP.

About 20%, 25% are moderate. They can be treated with either DDAVP or a factor concentrate. And one in 500,000 very rarely are severe, type 3.

Next slide. So in hemophilia there was actually a plenary lecture at this year's world conference, 45 minutes on what is a bleed. And it's a subject of discussion for many years.

If you have hemophilia and you have a bleed you will know you have a bleed. You get what I can only describe as an aura, a feeling at the joint or muscle that's followed pretty quickly by pain, by heat, by swelling as blood escapes into the joint or muscle. And, obviously, this pain, heat and swelling, the blood escaping into the joint causes a lot of damage. If you don't get early treatment you get a lot of joint damage and subsequent arthropathy.

Next slide. The vast majority of bleeding episodes, so when you talk to people on the street and you mention hemophilia sometimes they will think, well, this is somebody who will bleed to death from the slightest cause. That's nonsense, because if that was the case everybody with hemophilia would have a beard, we wouldn't dare shave.

The fact is that if you get a nosebleed you won't bleed any faster than normal. But it won't stop as quickly. But you can put pressure on that.

The main problem with hemophilia are bleeding into joints and muscles. So about 70% to 80% of the bleeding episodes are into joints and muscles. About 10% to 20% into muscles or soft tissues. Other major bleeds can be 5% to 10% and central nervous system bleeds such as brain bleeds or bleeds into the spine are less than 5% but obviously are life-threatening.

Next slide, number 20. So when we look at joint bleeds, the most common bleeds are knee bleeds followed by elbow, ankle, shoulder and then wrist and hip are very small proportion. If you look at countries where there is untreated hemophilia or substantially untreated hemophilia you will very quickly notice the knee joints of the boys and young men are very, very badly damaged. So knees, elbows and ankles are where you notice the most damage.

Next slide, 21. And you can see here some examples of recurrent bleeding into knee joints in hemophilia.

What happens is without treatment you get recurrent bleeding episodes that cause more and more damage to the joints and eventually joint deformity and a condition called hemophiliac arthropathy. And it's very, very common, in fact, for people with severe hemophilia who have not had adequate treatment throughout their life to require orthopedic surgery, joint replacement over many years.

Next slide. And here you can -- these are some photographs I've taken in various countries around the world over the years. These are typically boys with severe hemophilia who have not had access to any sort of adequate factor replacement therapy.

You can see the two boys at the bottom, these were Belarus in India, you can see their knee joints are already destroyed at a very young age. And the boy in the top left-hand corner, this was taken in Peshawar, Northwest Pakistan and this child had traveled for six hours with his father on a bus over rough roads to get treatment for a bleed in his face and a bleed in his arm. And, of course, the treatment he received was so substandard that he probably caused more damage with the journey than was ameliorated by the treatment he actually received.

So the principles of treatment for hemophilia, you can obviously see how much damage this untreated bleeding does to joints and muscles and they can be life-threatening or certainly limb threatening. So preventing bleeding ideally is the case, but you have to treat bleeds early. And the key to treating bleeds early is home treatment because if a person who needs -- the treatment is with an injection of the missing factor concentrate, if the individual gets a bleed into their joint or their knee, for example, and they have to travel to the hospital and wait for treatment it can be a delay of several hours of which at which time the bleed is well-established in the joint.

Home treatment means early treatment and that is actually what you want to do. You want to treat the bleed as soon as that aura starts, as soon as the individual starts feeling some discomfort in the joints. Obviously, if you have severe bleeds they need to follow up treatment in hospitals.

People with hemophilia have to avoid aspirin, these cause stomach bleeding. They have to avoid intramuscular injections, these can cause bleeds and they cannot use non-steroidal anti-inflammatories.

On-demand treatment is the name that we give to treatment where the treatment is administered to treat a bleeding episode. So it is reactive. When you get a bleed in a joint or a muscle you treat, obviously you treat as quickly as possible.

Prophylaxis is the preferred method of treatment where you treat the person with hemophilia either three times a week for Factor

VIII deficiency or twice a week for Factor IX deficiency. You maintain the factor level of greater than 1% at all times and this actually prevents spontaneous bleeds for the most part and prevents a lot of the joint and muscle damage.

Next slide. So the development of replacement therapy, in the 1960s you had plasma and cryoprecipitate were the mainstays of therapy. The problem with these was that you had to give a very large volume to get a small amount of factor concentrates.

In the 1970s they developed a method of concentrating this missing clotting factor into so-called plasma-derived clotting factor concentrates. And this for the first time you could give a lyophilized vial of medication where you can give a large amount of treatment in a relatively small volume and really titrate or calibrate the treatment you were giving.

Unfortunately, that led from the 1970s up to the early 1990s a lot of the products used were made from plasma pools which were contaminated with HIV or hepatitis C. And this resulted in the death of thousands of people with hemophilia in many countries around the world and the infection of many more.

From 1985 they developed a virally-inactivated plasma-derived coagulation factor concentrates so that by the end of the 1980s they could ensure that HIV and hepatitis C and indeed hepatitis B were no longer transmitted. In 1994 we had the advent of recombinant or synthetic coagulation factor concentrate and from 2014 a whole new generation of extended half-life coagulation factor concentrates which effectively means that the coagulation effect of the medicines last longer in the blood. In the case of Factor VIII they typically last 1.5 times longer, in the case of Factor IX between three and five times longer than the current recombinant factor concentrates.

This picture here next slide, slide 25, these are two boys getting cryoprecipitate at a hospital in Chile. And this is a slow process with a large volume product.

Next slide. This was a child in Sweden at a summer camp self-infusing with factor concentrate. But, of course, you can see if you look at the size of the syringe it's quite a large volume. This was an early plasma-derived factor concentrate.

Next slide. This is a more modern factor concentrate which is easier to infuse and a much smaller volume and lends itself very readily to home treatment.

And I think at this stage, that's slide 27, there is now a video clip if we can start the video. And this is an 11-year-old boy in Ireland, Adam, and this video shows Adam self-infusing with factor concentrate at home.

And you might perhaps let me know when that has finished. As you can see it actually takes, it's lot of effort, takes a lot of training to train a child to be able to self-infuse intravenously. It's not easy to self-infuse intravenously.

(video playing)

Is the video finished?

Josh Brodsky, Alnylam Pharmaceuticals, Inc. - Associate Director, IR & Corporate Communications

Yes, you may proceed, Brian.

Brian O'Mahony, Irish Haemophilia Society Ltd. - Chief Executive

Okay, so slide 29. So the current treatment options, cryoprecipitate and plasma, our options it's still in some developing or emerging countries but only in the absence of factor concentrate as an option. They are not really good therapeutic options.

Plasma-derived factor concentrates are still widely used for Factor VIII, Factor IX, von Willebrand's and for many of the rare bleeding disorders. And, in fact, for von Willebrand's or for most of the rare bleeding disorders there are currently no recombinant alternatives. There is a recombinant von Willebrand's under development, there is a recombinant Factor XIII but for most of the rare bleeding disorders you are still using plasma-derived factor concentrates and in some cases there are not single factor concentrates that you can use.

You are using a combination of several or even plasma. Recombinant factor concentrates are available for Factor VIII, Factor IX and Factor XIII; DDAVP, which is a synthetic hormone, is available for mild hemophilia; and extended half-life factor concentrates are available for Factor VIII and Factor IX deficiency.

In terms of my personal patient journey, well, I was born in 1958 so when I was growing up there was no treatment. You got whole blood on occasion and it wasn't until I was into my late childhood, early teenage years that I first started to get plasma and then factor concentrate. So I went from the year of no treatment to blood to plasma to plasma-derived factor concentrate and then in the late -- the plasma-derived factor concentrates from the mid-1970s and then it was actually the late 1990s before we had a recombinant Factor IX concentrate.

And that has been the treatment since then. It has not stopped me getting an education and walking and having a full quality of life. But certainly with the advent of much better replacement therapy and much more aggressive treatment it has become much easier to live with severe hemophilia.

Next slide, 31. The European Haemophilia Consortium of which I am President is a consortium of all 45 of the European national hemophilia societies. And we have a number of objectives we try to support and empower our national member organization, so we see our role very much as developing the tools that our organizations can use nationally to advocate for better treatment and care.

We promote access to optimal treatment and comprehensive care. We ensure that we have constructive engagement with key stakeholders at all the European institutions. We've tried to make sure that we influence European policy and, obviously, we have good governance and sustainability is, obviously, a requirement.

Next slide, 32. We've run a lot of training workshops over the years, so we have just finished a whole series of workshops on economics and health technology assessments where we train the patient organization leaders now to do this. We have a workshop every year in new technologies where we explain proactively to the organizations the pipeline products that are currently under development so that they are ready for these, so that they are looking at these, so that they are engaging with the health authorities and with the paying authorities prior to products actually coming on the market.

We are currently starting a whole new series of workshops on tenders and procurement where we try to train them on the importance of patients and clinicians being involved in the procurement for their medication. We develop young people, we develop leaders and we have a specific leadership development program where we bring together young leaders with the current leaders. We have a European inhibitor program where we bring together people with inhibitors from the all European countries.

We produced policy reports for our national organization and the EU policy four times per year. And we have an annual scientific conference.

Next slide. We collect and publish data annually and our data collection is very important to us. And since 2009 we have looked at every aspect of hemophilia treatment and care in every European country, and we've looked at this in 2009, 2012 and 2015, so we are looking at how this progresses over the years so we're able to see the changing hemophilia environment in Europe.

In 2014 we carried out of full survey of tenders and procurement system in all the European countries. And this year we're doing a survey on hepatitis C and hemophilia.

There was also a certification system for centers in Europe. So hemophilia treatment centers can be certified as either top level comprehensive care centers, which must have at least 40 patients with severe hemophilia who regularly attend, or European hemophilia treatment centers who must have at least 10 patients who regularly attend. The entire model of treatment of hemophilia is based around comprehensive care at expert centers and the EHC are involved in the body with certify centers.

We have a medical advisory group who issue proactive statements on important issues with a very fast turnaround. And we have a significant input into drafting of the Council of Europe recommendations on hemophilia. Because of our data collection we have found that we actually have the evidence that's required to put forward recommendations for the Council of Europe meetings.

If you look at the next slide, 34, this is an example of some of the data we have collected where we look at every aspect of hemophilia care in Europe. And the next slide 35 here we look at Factor VIII use per capita versus GDP. And this is some of the data from 2014, and you can see it's not a straight-line progression.

So you can see some countries where their Factor VIII use is greater than you would expect given their GDP. For some countries it's less. And this is very much a function of the strength of the patient organization collaboration with doctors and the success or lack of success of their advocacy efforts.

Next slide. And here, what you can see here, however, is an encouraging trend towards increasing Factor VIII use in Europe between 2008 and 2014 from the three surveys we have carried out. So we are seeing a general increase across the board and we try to encourage this increase by making sure that the recommendations from the Council of Europe are such that they can actually help countries to get to the next level of care.

Next slide, 37. We carry out roundtables of stakeholders, so we carry out three or four roundtables every year, at least two of these are hosted in the European Parliament. So we bring together the members of the European Parliament, the EU Commission, industry, clinicians and patients and for 2016 our roundtables will be on inhibitors, hepatitis C, aging and outcome measures.

In terms of representation we're formally represented on the EMA on the Committee for Orphan Medicinal Products and the European Commission Expert Group for Rare Diseases and the European Parliament MEP group and the Council of Europe and EDQM meetings. We do a lot of World Hemophilia Day events and we have newsletters which we produce three times per year.

So if I look at the future, the future the year I was born was peanuts. I was force-fed peanuts for about a year by my parents when they read some article Woman's Home Journal from the states which said that peanuts were good if you had hemophilia. They actually don't do you any good at all if you have hemophilia, but they do have the long-term result that I hate peanuts.

So what do people with hemophilia want? What they want is to avoid or prevent bleeds or even small microbleeds that can still damage the joint in the absence of pain. They want to treat bleeds effectively and with minimum disruption when they occur.

They want to be able to lead a normal life and engage in normal activities. And I'm not talking about extreme activities, I'm talking about normal everyday activities. They want treatment that is safe and effective, especially given the horrendous history of the past and they want treatment that is convenient and easy to administer.

Next slide. They want an oral treatment, although that's not currently feasible. If not they want a subcutaneous treatment.

They want less frequent intravenous infusion. Your veins are precious and it's very hard to intravenously infuse yourself three times a week, week after week, month after month, year after year without your veins giving out. They want treatment that lasts longer and gives higher levels of protection.

They want treatment designed with patients in mind as end-users, not clinicians or nurses. This is something that has often been the case that even the packs used for home treatment are designed and the focus groups tend to be doctors and nurses who don't use these at home. They want to go from a severe form of hemophilia, less than 1%, up to at least a mild form and they want the possibility of a cure by gene therapy.

Net slide. Ideally the treatment options would be non-intravenous, they'd be safe and effective. There would be better treatment options for inhibitors, because inhibitors certainly, people with high titer inhibitors which are antibodies to the factor where the factor doesn't work, their treatment options are severely limited and their quality of life is back where ours was in the 1970s.

We need more treatment options for von Willebrand's and for rare bleeding disorders, we need treatment that minimizes the disruption of the person's life and we also need treatment that's economically sustainable to allow access to treatment by payers. It's worth noting that recombinant factor concentrates have been around since 1994, but the vast majority of countries still can't afford these because they are not economically viable for them.

Thank you.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Thank you, Brian, for sharing your very unique perspective on hemophilia as a patient, patient advocate and as a scientist. So just building on what has already been presented, there has been tremendous progress made in the management of hemophilia over the past few decades. However, significant unmet need still remains in all patient segments.

Prophylactic replacement factor therapy can be very effective for those who have access to therapy. However, we should recognize that this is a therapy with tremendous treatment burden for patients, their caregivers and their family members. There are complications that can arise from repeated IV access, as we've heard from Brian, and the heavy burden of therapy can lead to reduced compliance which can result in suboptimal real-world efficacy which ultimately is what counts.

Inhibitor patients, those who have developed inhibitory alloantibodies to replacement factor, represent a group of patients with very high unmet need, patients who are more challenging to manage and a group that for the most part has been left behind when it comes to enjoying the benefits of an effective prophylactic therapy. Finally, there are segments of patients with rare bleeding disorders with high unmet need who may have severe bleeding phenotypes but with little or inadequate prophylactic therapy options.

Fortunately for patients with hemophilia, today is truly an exciting time with numerous innovative approaches in development for the management of hemophilia. And these include modified replacement factor therapies. These are therapies where the factor has been engineered to extend half-life.

Also includes gene therapy where there's been significant progress over the past decade on gene vector engineering and also engineering of the expression cassettes. And we're now beginning to see some of the very early promising clinical data with the gene therapy approaches.

There is also tissue factor pathway inhibitor or TFPI inhibitors. These are agents that block TFPI which is an inhibitor of the initiation of coagulation. And so these approaches might be a way to promote coagulation.

There are bispecific antibodies highlighted by emicizumab or ACE910 which is a bispecific antibody that mimics the cofactor role of Factor VIII, thereby promoting thrombin generation and improved coagulation. Finally, there is an RNA interference therapeutic approach fitusiran which we're going to be talking more about today which is an RNAi therapeutic that targets antithrombin as a means to increase thrombin generation and improve hemostasis. The diversity and the promising nature of all these different approaches is undoubtedly a good thing for patients and we at Alnylam are excited to be participating in this emerging therapeutic landscape.

So if we now turn our attention to fitusiran, just a little bit of background on what that is. It's a subcutaneously administered small interfering RNA that targets antithrombin and as discussed before it harnesses the RNAi mechanism for regulating plasma antithrombin levels. And the therapeutic hypothesis is really founded on the understanding of hemophilia A and B as ultimately as disorders arising due to ineffective clot formation due to insufficient thrombin generation.

Thrombin, as you can see by the very simplified coagulation cascade depicted on the right-hand side, is the key terminal enzyme of the coagulation cascade that converts soluble fibrinogen in the blood into insoluble fibrin which ultimately forms the mesh that forms a blood clot. In hemophilia, deficiencies in Factor VIII or Factor IX upstream of thrombin result in insufficient thrombin generation.

Now what we aim to do with fitusiran is to lower the levels of antithrombin, which as its name suggests is a key inhibitor of thrombin as well as other members of the coagulation cascade. By lowering antithrombin levels the aim is to promote sufficient thrombin generation to restore hemostasis and prevent bleeding. We've been inspired or guided in this therapeutic hypothesis by human genetic evidence or observations that have shown that in patients who have co-inherited thrombophilic traits, these are traits that promote thrombin generation in the background of hemophilia, appears to ameliorate the bleeding phenotype.

Now just to summarize some of the emerging features for fitusiran, it is not a biologic, it is not made by human products or animal cell lines. It's a manufactured RNAi therapeutic. There is no reconstitution or mixing required.

It's a formulation that is stable at room temperature so there's no cold chain requirement. It's a molecule that's administered subcutaneously as opposed to intravenously. It has a long duration of action and as Benny will discuss soon, it's currently being evaluated in Phase 1\2 studies as a once-monthly dose.

Of course, it is not a factor and, therefore, may help avoid inhibitor formation due to reduced factor exposure or reduced intensity of factor exposure. Those are two elements that are known to increase the risk of inhibitor formation.

Finally, the mechanism of fitusiran is directed at addressing the ultimate thrombin production defect and, therefore, may be amenable to both hemophilia A and B including those who have developed inhibitors and potentially other rare bleeding disorders. So we think these emerging attributes have the potential to address many of the unmet needs in hemophilia. So we're quite excited about what fitusiran may be able to offer patients in the future.

With that, I will turn it over to Benny to talk about the most recent clinical results. Benny?

Benny Sorensen, Alnylam Pharmaceuticals, Inc. - Senior Director, Clinical Research

Thank you, Akin. I will start with an overview of the Phase 1/2 study we have been undertaking and it's a study in now four parts where part A was the single ascending dose investigation in healthy volunteers that has been completed and following that we transition to part B which was a multiple ascending dose study where we dosed fitusiran subcutaneously weekly in patients with hemophilia A or B without inhibitors.

From part B we learned that fitusiran had a duration of effect that would support transitioning to a monthly dosing regime which we have been studying in part C as a multiple ascending dose monthly dosing study again in patients with hemophilia A in B. And today's presentation will provide a lot of insight to what we had learned from part C. Very recently we have transitioned now to part D where we are investigating fitusiran in hemophilia A and B patients with inhibitors, and you can see here that we are now investigating fitusiran on a monthly fixed dosing regime.

On the next slide, slide 49, there is an overview of the demographics and baseline characteristics of patients enrolled in parts B, C and D. What's of note here is that we are enrolling both patients with hemophilia A and hemophilia B. The majority of patients enrolled suffer from severe hemophilia, a few patients with moderate hemophilia from a biochemical point of view. However, phenotypically these patients look like severe patients.

On the next slide, slide 50, is an overview of the safety and tolerability from parts B, C and D. There's been no serious adverse events related to the study drug and the majority of AEs have been recorded as mild and moderate in severity and the majority of the AES seen in more than 10% of patients has been upper respiratory tract infections as well as joint pain which is common in patients with hemophilia.

11 patients, 35%, has reported a drug-related injection site reaction. All of these have been mild, self-limiting, characterized by pain and redness at the injection site not requiring any additional intervention. One patient discontinued due to an AE of non-cardiac chest pain that was considered severe and possibly related by the investigator.

This was preceded by a gastrointestinal infection and increases in CRP and then associated with transient elevations in ALT, AST and D-dimer. There was no increases in total bilirubin.

We undertook extensive evaluation. All of that was unremarkable. And venous thromboembolism, in particular, was excluded by a serial high sensitivity CT angiograms as well as ultrasound scans of both liver and lower extremities. This event resolved with just symptomatic management including antacids and analgesics.

There's been no thromboembolic events or laboratory evidence of pathologic clot formation as assessed by a combination of D-dimer platelet count fibrinogen and/or PT/INR and with the exception of the case noted above no other clinical significant drug-related changes in laboratory parameters. Importantly, there's been no instances of anti-drug antibody formation and the bleed events that occurred were successfully managed within fusion of standard replacement Factor VIII or Factor IX or bypassing agents.

On the next slide, slide 51, let's have an initial look at the pharmacodynamic effects of fitusiran. This illustrate antithrombin lowering in part C following a monthly dosing of fitusiran. On the y-axis you can see the percentage mean antithrombin activity relative to baseline and on the x-axis you see the days since the first dose, so time.

And you can see that fitusiran is characterized by having an onset period of approximately 28 days and after that we see a dose-dependent antithrombin lowering that is durable and sustained and, therefore, supportive of the monthly dosing regime that we are exploring. You can also see that the way we have investigated the efficacy of fitusiran is looking at an observation period that extends from day 28 up to day 112.

On that the next slide, 52, we are illustrating the dose response, the dose-dependent antithrombin lowering in a slightly different manner. We are now looking at the mean maximal AT lowering in each dose cohort from both part A, part B and part C. You will appreciate that there is dose-dependently lowering of antithrombin with fitusiran.

And when we get to a 450, 900 micrograms per kilogram monthly and 1,880 milligrams monthly -- and 80 milligrams fixed dose monthly you see a plateau effect where there is a decreasing inter-individual variability. Particularly at the 80 milligram fixed dose the mean maximum AT lowering is 87% plus, minus just 1% variation.

Slide number 53, we are illustrating the thrombin generation results from parts B and C. And as Akin alluded to, hemophilia is a disease characterized by a defect thrombin generation. So what is key for fitusiran is to investigate to what extent we can correct and normalize thrombin generation when we lower levels of antithrombin.

On the left-hand side in this graph here you see the peak thrombin generation that's measured in healthy male volunteers. And on the right-hand side you can see quartile reduction of antithrombin lowering in patients with hemophilia A or B. What you see is an antithrombin lowering dependent increase in peak thrombin generation and the mean thrombin generation increase is approximately 300% relative to baseline at AT lowering of more than 75%.

Also of note it is important to see the number of subjects and the number of measurement points where a patient had peak thrombin generation within the range of healthy normal volunteers. Also important to note is that none of the peak thrombin generation measurements exceeded the upper range of that recorded in healthy volunteers.

In the next slide here we are trying to estimate what that increase in peak thrombin generation achieved with fitusiran, what that corresponds to in factor levels. What's shown here is that the peak thrombin generation increase achieved with fitusiran is equivalent to maintaining Factor VIII trough levels above 40%. We've investigated this in a subgroup of the subjects participating in the study.

These subjects, they were administered a dose of Factor VIII of 50 units per kilogram prior to starting treatment with fitusiran. What you can see here in the gray bars of these three individual and the open squares is the peak thrombin achieved with infusion of Factor VIII. And you can see it's characterized by a prompt peak and a rapid decline in peak thrombin generation.

What you also then can see is as we lower levels of antithrombin, we increase peak thrombin generation. And the increase in peak thrombin generation in these three individuals in all of those cases exceeds that that corresponds to 40% Factor VIII. Also it's important to notice that the increase in peak thrombin generation is stable and sustainable over time.

So on slide 55 with the reduction in antithrombin, with the increase in thrombin generation we have now started exploring the effects of antithrombin lowering on the estimated annualized bleed rate. What you see here is that with increasing lowering of antithrombin we see a decrease in the annualized bleed rate.

What's particularly important to note is in this is that for a subject, in this case 16 subjects who have spent time at antithrombin lowering of more than 75%, and to be exact 1,128 days, there was only 11 bleed events recorded. That corresponds to a median ABR of 1.

Before I go to show every single individual in part C here, on slide number 56 I want to remind everybody about the pharmacodynamic cost of fitusiran. So following the first injection of fitusiran you see the onset period of approximately 28 days before there is full pharmacodynamic effect of fitusiran.

As antithrombin is reduced we see an increase in peak thrombin generation. And in this case here we illustrate the importance of looking at the data as part of an onset as well as an observation period. For this particular subject you will appreciate that from day 28 to day 112 with the correction of peak thrombin generation achieved there was no bleed events occurring.

So in the next slide, slide 57, first I'll apology that this is slightly busy. However, we want to be very transparent in our experience with every single individual in part C. So on the left column you can see the dose of fitusiran administered and the first four cohorts were weight-based dosing 225, 450, 900 and 1,800 micrograms per kilogram and the last cohort was a fixed dose of 80 milligrams.

You can then see patient identification numbers as well as their prior treatment and PPx here is prophylaxis and OD is on demand. Then in the next column the pre-study annualized bleed rate that was achieved with their prior treatment. Then in the column called onset ABR is the estimated ABR during the first 28 days after starting treatment with fitusiran.

However, what's most important is to look at the last four columns which is characterized here as the observation period. First, you can see the number of bleeds in each individual as well as the estimated overall annualized bleed rate. Then there is a column counting out the number of spontaneous bleeds and the associated annualized spontaneous bleed rate.

I think what you will appreciate that the total number of bleeds that have occurred has been very few. And, in particular, as we look at cohorts dosed 900, 1,800 micrograms per kilogram or 80 milligrams fixed dose you will see that a majority of patients didn't experience any bleeds. Actually more than 70% had an annualized bleed rate of zero and only one subject experienced a spontaneous bleeding episode.

On the next slide we have summarized these efficacy estimates. And what you can see on the left is a summary of the median ABR of all cohorts in part C, the pre-study median ABR for patients previously treated with factor prophylaxis was 2 and patients previously treated on demand had a median ABR of 28.

Then during the onset period, the median ABR was 13 and during the observation period the median ABR was zero. If we take a close look at the median ABR estimate for the cohort treated at 80 milligrams fixed dose you can see that in these patients the prophylactic pre-study treatment resulted in a median ABR of 6 and, again, during the onset period a median ABR 13 and then in the observation period a median ABR of zero.

So to summarize for all cohorts in part C, 82% of patients reported no spontaneous bleed and 53% of patients reported no bleed. More than 70% of patients treated at 900, 1800 micrograms per kilogram or 80 milligram fixed dose had no bleed events.

So turning from the non-inhibitor part of the study to part D where we are now studying fitusiran in inhibitor patients, here the study population is hemophilia A and B patients with inhibitors utilizing bypassing agents for bleed management. And as similar to what we have done in non-inhibitor patients, prior to starting treatment with fitusiran we have done an exploratory pre-dose evaluation of response to the bypassing agent they are currently using. And plasma was then collected at certain time points before we started treatment with fitusiran.

What we will show here today is the first cohort enrolled and dosed at a fixed low monthly dose of 50 milligrams. Also we will instruct people that we have now enrolled second cohorts and they are being dosed at a monthly dose of 80 milligrams.

So slide 60 again is showing in a transparent manner what we have learned about antithrombin lowering and thrombin generation results in the first six patients with inhibitors. Comparable to what we've seen in non-inhibitor patients we see that antithrombin lowering is associated with an increase in peak thrombin generation. It's robust and it's sustainable over time. If we compare the thrombin generation that is achieved with lowering of antithrombin to the pre-study administration of bypassing agents we also seem to compare favorably with the peak thrombin that very temporarily can be achieved with infusion of a bypassing agent.

Then on slide number 61 we have a table that shows the preliminary outcomes of dosing with the low dose 50 milligrams of fitusiran. You can see the patients with hemophilia A and hemophilia B with inhibitors all being previously treated on demand with either recombinant Factor VIIa or plasma-derived aPCC.

What you will note here is that these patients have very significant pre-study annualized bleed rates all the way up to 80 bleed events a year. Already during the onset period there appears to be a substantial reduction in that bleed frequency. And then during the observation period what we have seen is that two out of five subjects that had evaluable results achieved an ABR of zero and the others had at least 50% reduction in the pre-study ABR.

Third, a follow-up is ongoing to continue exploring both safety and bleed efficacy with the longer-term dosing and all eligible patients have rolled over to our extension Phase 1/2 extension study. As mentioned before, the second cohort dosed at 80 milligrams is currently in follow-up.

So in summary, fitusiran has generally been well tolerated in hemophilia A and B patients with and without inhibitors. There's been no serious adverse events related to study drug, no thromboembolic events and the AES occurring in more than 10% of patients have been characterized by upper respiratory tract infections and joint pain and the majority of these mild and moderate in severity.

11 patients have reported mild and drug-related injection site reactions and there's been one discontinuation due to an AE. However, this event resolved which is symptomatic management.

There is evidence of clinical activity and potential correction of the hemophilia phenotype in non-inhibitor patients. We see dose-dependent AT lowering and increase in thrombin generation with our once-monthly subcutaneous dosing regime and in particular focusing on the 80 milligrams fixed dose we see consistent AT lowering above 75%.

And with that we have seen that fitusiran could achieve a median ABR of zero with 53% of patients being bleed free and 82% of patients experiencing zero spontaneous bleeds. We believe that these data are encouraging and also the data that are emerging now in inhibitor patients are very encouraging. We see similar to non-inhibitor patients that AT lowering is translating to an increase in thrombin generation and the exploratory post hoc analysis shows so far 49% to 100% reduction of bleed at the initial low 50 milligram dose and the second cohort of 80 milligrams fully enrolled and we will be able to report on that later in the year.

Just to outline a few next steps for the fitusiran program. As of July 11, we had 21 patients enrolled into an open-label Phase 1/2 extension study and that includes both non-inhibitor and inhibitor patients. We believe we will have additional data to share late 2016, likely at ASH pending abstract approval, and that will include updated results from parts C and D of the ongoing Phase 1 study and we will also be able to present initial results from the Phase 1/2 open-label extension study. Then we plan to advance to pivotal studies in early 2017.

Just want to give a brief view of how the Phase 3 designs are expected to look like in the beginning of 2017. In principle we are looking at conducting two pivotal studies: one in hemophilia A and B patients with inhibitors and another in hemophilia A and B patients without inhibitors. We expect to enroll these in an open-label fashion and randomize them to fitusiran or to maintain their current standard of care use of on-demand treatment.

As previously with the development of drugs for treatment of hemophilia, the primary endpoint will be the annualized bleed rate and the total number of bleeds as well as the consumption of bypassing agents and/or Factor VIII or IX consumption. And we will extensively investigate also quality of life and, of course, provide a description of safety and tolerability.

With that, we will be more than happy to take questions and answers. And Akin, over to you.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Great, thanks, Benny. So we will now move on to the question-and-answer portion of the roundtable. And thank you to many of you who have already submitted your questions.

So if you'd like to ask a question to Brian, Benny or to me, please you can again submit them by clicking the ask a question button located above the slide window on the webcast player. So maybe I will start and put the first question to Brian.

I think historically people generally know that in hemophilia people have been rather loyal to their products and have not typically switched products quite frequently. How open do you think people with hemophilia are going to be to some of these new emerging therapies? What would make a patient or physician to decide that they might want to switch from their current therapy?

Brian O'Mahony, Irish Haemophilia Society Ltd. - Chief Executive

I wouldn't agree that there's enormous loyalty. People tend to switch products reasonably frequently if it's a national decision. I think it depends on, obviously, given the history of the past with HIV, hepatitis B, hepatitis C safety is always a major requirement.

So I think when any patient or indeed any doctor or system is looking at a new product they look at safety, they look at efficacy, they also look at cost. But I think that there's more likelihood that people will change, will be open to change where the decision is made not by an individual patient or by an individual doctor in a center but by a consensus within the country.

So for example by MASAC or the United Kingdom doctors or European group, they tend to look at these things. In situations where you are relying on individual doctors and individual patients to make the decision and I think change can be slower. But I think people are quite open to change.

There's a lot of knowledge out there in the community broadly about pipeline products and I think people are open to change. But I think that the criteria they will be looking at will be safety, will be efficacy, will be its impact on their quality-of-life and for the doctors and for the payers it will be the sustainability of the cost of the new products.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Great, thank you, Brian. Maybe just following up on that a little bit more, you touched upon a number of things that patients and their physicians and family members are looking for.

But if you had to comment a little bit more on that in terms of what you think is going to be most important to the patient community? Is it treatment frequency, the route of administration, risk of inhibitor formation or perhaps some other attributes? Can you talk to that a little bit?

Brian O'Mahony, Irish Haemophilia Society Ltd. - Chief Executive

I think all three of those are important. I would say route of administration and risk of inhibitor formation. Even the plasma-derived products for the last 20 years have been safe, so the viral contaminations for the most part are a thing of the past, although there are always new emerging viruses, most notably Zika at the moment.

So the biggest safety risk at the moment from factor concentrates from the current treatment is the risk of developing an inhibitor. If you develop an inhibitor it's quite a serious complication and it can damage your quality of life significantly.

I would say route of administration is very important. People have been using intravenous infusion since the 1960s, so having an alternative route of administration I think is really important. And that, in fact, is probably more important than treatment frequency because the treatment frequency is entirely associated with intravenous infusion.

So if you have the extended half-life factor concentrates which are relatively new in the market, one of the big advantages seen with those is lower frequency of infusion because it's intravenous. If you had a subcutaneous route of administration the frequency is not as important.

If you had oral similarly it's not as important. So I would say route of administration and inhibitors.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Okay. And maybe just to get your own personal perspective, again you took us very nicely through your personal history starting with really no therapy to today. In your view what has really been the biggest advance in hemophilia care that you have experienced in your lifetime?

Brian O'Mahony, Irish Haemophilia Society Ltd. - Chief Executive

Without question home treatment, the ability to treat a bleeding episode as soon as you feel it starting. That's really important and that's still not the case actually in many countries. So factor concentrate you have big improvement, recombinant over plasma-derived big improvement, but home treatment, the ability to treat quickly was the biggest single improvement.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Great. Okay, now I think Brian here's another question for you at one of the emerging therapies. So with the gene therapy approach, and various companies are working to express Factor VIII for hemophilia A, so far there has been inter-patient variability with factor expression using a gene therapy, and how much is the into patient variability and factor expression of concern for the physician or the patient ultimately?

Brian O'Mahony, Irish Haemophilia Society Ltd. - Chief Executive

I think there was more reassurance about the Factor IX gene therapy at the recent WFH Congress where one of the papers showed a very tight level of expression in the first several patients. They were all around 30%, whereas with the Factor VIII gene therapy you had an enormous variation from practically no expression to over 150%, in fact getting to the point where you were worrying that the expression might be too high and perhaps developing a risk of thrombogenicity.

I think it's still early days with gene therapy products. I think you will want to see more sort of definite and consistent expression and also you'd want to develop an understanding of why there's such enormous variation in expression at the same dose. But that is a concern. At the same time, it's better than seeing no expression.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Okay great. Thanks. This is a question, I think Brian maybe I will start off with you and Benny you can also comment, as well.

So do you have a point of view on the risk that recombinant Factor VIII would generate more inhibitors in severe hemophilia A versus the plasma-derived? That question is really I think alluding to the recent SIPPET study results.

Brian O'Mahony, Irish Haemophilia Society Ltd. - Chief Executive

The SIPPET study, yes. I think the results of the SIPPET study which showed an 87% higher risk of inhibitors with recombinant compared to plasma-derived, the fact that recombinants were associated with a higher risk of inhibitors I don't think was a surprise to most people in the community.

What was a surprise was the very high percentage of patients who had inhibitors with both. So it was about 44% with recombinants and about 23% with plasma-derived.

Now if you look at previous meta-analysis bringing together lots of different studies, and I point out that the SIPPET was a randomized controlled trial so it's better data. But the previous meta-analysis of previous studies showed a similar increase in recombinant over plasma-derived, albeit the total percentage getting inhibitors was lower.

So I think the trend is probably correct. I think clearly recombinants are associated in my mind with a high risk of inhibitors.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Benny, do you have any more to add?

Benny Sorensen, Alnylam Pharmaceuticals, Inc. - Senior Director, Clinical Research

Yes, I think I agree with you, Brian. I think the only other thing to add is the learning that using a plasma-derived Factor VIII concentrate is not going to solve the problem.

There is still way too many of these patients developing an anti-drug antibody to Factor VIII irrespective of whether it's plasma-derived or recombinant. So I think if anything it emphasizes the importance of trying to develop totally new treatment paradigms for management of hemophilia.

Brian O'Mahony, Irish Haemophilia Society Ltd. - Chief Executive

I totally agree. Are these the meta-analysis or are the other one is 20% to 40% of the inhibitors. That's an unacceptably high percentage.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Agreed. Now I guess pose a few questions to Benny.

First of all, can you talk a little bit about patients who were administered factor to treat bleeds during the fitusiran Phase 1 trial and a little bit more about how much factor was used? And were there any issues that were encountered during the process?

Benny Sorensen, Alnylam Pharmaceuticals, Inc. - Senior Director, Clinical Research

Sure. So I think before I start it's important to acknowledge that the number of bleed events that really have recurred when antithrombin lowering has been more than 75% has been very few. So just to remind all, only 11 bleeds occurred in 1,128 days.

So in totality, the amount of experience we have here it is not extensive. Yet the bleed events that did occur when antithrombin was lowered more than 75% overall was mild and was managed with just one or two injections of Factor VIII and IX.

The dosages of Factor VIII and IX was really in the lower end of what is recommended by the WFH for management of bleed events. And just for those not aware, WFH have a guideline for how to manage mild to moderate and severe bleed events. And the bleed events are occurring for patients on fitusiran has all been managed as very mild bleed events and dosed accordingly with factor ranging from 5 to 20 units per kilogram.

There's been no adverse events associated with that factor administration. The response has been prompt and has been assessed by the patients as better than or as good as their previous standard management of breakthrough bleed events.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Great, thanks. Now just somewhat related to that there is a question about the combination of antithrombin lowering and factor replacement. Benny, could that lead to major thrombotic risk and particularly in the setting of emergencies, would it be risky in that setting to administer factor on top of background fitusiran in that situation?

Benny Sorensen, Alnylam Pharmaceuticals, Inc. - Senior Director, Clinical Research

It's a great question. I think there is a certain degree of complexity associated with emergency and trauma that makes it difficult to make one guidance here. But let's walk through what would happen if a patient was traumatized.

So a patient on fitusiran experiencing the expected robust, sustained pharmacodynamics effect would increase and thrombin generation all other things equal upon the trauma they will at that time point be substantially better protected against serious bleed events occurring as part of that trauma. Now standard would be that the patient would be admitted to an emergency room and there knowing that the patient has hemophilia they would likely get an infusion of Factor VIII or IX or bypassing agents.

Now what we know already from pre-clinical experiments and the little clinical experience that we also have is that Factor VIII and IX as well as bypassing agents are really extremely short-lived. So the peak point only lasts for very few hours. After that there is a rapid decay in the factor and the rapid also decline in that additional thrombin that could be produced.

So as of now we don't have experience but we don't believe based on the pre-clinical data we have as well as the clinical data we have that there would be any substantial risk associated with a single or a few infusions of Factor VIII and IX. I think most

importantly it's important to notice that patients who actually will be traumatized while they are on fitusiran have a better chance of actually having a hemostatic system that will protect them against experiencing exsanguination.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Okay. Benny, so now maybe shift gears a little bit and talk about D-dimer. So how do you explain the D-dimer elevation and the patient who discontinued and what does it mean to say there was no evidence of pathologic clot formation if D-dimer was elevated in that individual?

Benny Sorensen, Alnylam Pharmaceuticals, Inc. - Senior Director, Clinical Research

That's a good question. Let's separate them out.

So let's take the individual case that was discontinued. So just to walk through the case again, so this AE of non-cardiac chest pain, it was preceded by a gastrointestinal infection as well as measurable increase in CRP and then it was associated with elevations in liver function test as well as D-dimer.

Now the D-dimer in a case like this where we were thoroughly investigating for venous thromboembolism is likely to more reflect inflammation than clotting. That is really what is known about D-dimer. D-dimer is a highly sensitive biomarker for inflammation.

And in a case where there is preceding gastrointestinal infection as well as a preceding increase in C-reactive protein, the safety review committee assessed that the D-dimer increase we observed in that patient was not linked to clotting but was linked to inflammation. When we then later said that there was no signs of pathological clot formation is because the D-dimer is not a standalone biomarker of pathological clot formation.

The D-dimer must be assessed together with changes in platelet count, changes in fibrinogen, changes in PT/INR. And only if there is in combination all changes towards what we characterize as pathological, so reduction in platelet count, reduction in fibrinogen, increase in PT/INR, that is when the D-dimer is assessed in combination with these as being pathological. And we have not seen anything like that in that this study.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Thanks, Benny. Another question more on the pharmacology, in terms of the 80 milligram fixed dose, is the dose level similar to the 900 microgram per kilogram dose or the 1,800 microgram per kilogram dose?

The data would suggest you want to be close to the 1,800 microgram per kilogram weight-based dose but 80 milligrams would seem to be closer to the 900 microgram per kilogram dose. Yet the 80 milligrams and 1,800 microgram per kilogram data look more similar. So Benny can you talk a little bit about dosing and dose levels?

Benny Sorensen, Alnylam Pharmaceuticals, Inc. - Senior Director, Clinical Research

Yes, I think the way that we have illustrated the data there seems to be a difference between 900 and 1,800 micrograms per kilogram and 1,800 micrograms per kilogram seem to look like 80 milligrams. Now 80 milligrams roughly is 1,100 micrograms per kilogram in a patient. Honestly, with the exception of one outlying measure in 900, 1,800 and 80 milligrams are really very, very comparable.

So the 80 milligrams looks more like on average 1,100 micrograms per kilogram dose. And that leaves us with safety margin up to 1,800 and still leaves us the flexibility of having one fixed dose for all adults and adolescents which we think is a favorable profile to proceed with as we go into Phase 3.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Okay. Great. So now we've had some questions about rare bleeding disorder, so maybe this is again to you Benny, can you just say a little bit about how we think about the opportunities for fitusiran in rare bleeding disorders and also are there potential opportunities for fitusiran in platelet disorder?

Benny Sorensen, Alnylam Pharmaceuticals, Inc. - Senior Director, Clinical Research

So we strongly believe that fitusiran can play a key role in management of rare bleeding disorders such as Factor V deficiency, Factor VII deficiency, X deficiency, XI deficiency and we have pre-clinical data supporting this, as well. I think on the other note on platelet disorders there is already a clinical validation that improving thrombin generation in certain platelet disorders such as Glanzmann's thrombasthenia or Bernard-Soulier can have a favorable effect on bleeding tendency. So we will as we progress with clinical development pay increasingly attention to both rare bleeding disorders including primary hemostatic defects such as platelet disorders or type 3 von Willebrand's disease.

Akin Akinc, Alnylam Pharmaceuticals, Inc. - VP, General Manager, Fitusiran Program

Great, thanks, Benny. And I think now I will just hand it back over to Josh.

Josh Brodsky, Alnylam Pharmaceuticals, Inc. - Associate Director, IR & Corporate Communications

All right. Thanks, Akin, and thanks to you Benny and also thank you very much to you, Brian, for your perspective.

This concludes our RNAi Roundtable for today. The replay and slides will be posted on the Alnylam website later today at Alnylam.com/roundtables with the transcript to follow shortly thereafter. You can also visit that page to view bios of this event's speakers.

We look forward to your participation on Wednesday, August 31 at 11 a.m. Eastern Time as we discuss our ALN-CC5 program in development for the treatment of complement-mediated diseases and in the weeks that follow to discuss additional programs from Alnylam's pipeline of investigational RNAi therapeutics as shown on slide 66. For more details please visit www.Alnylam.com/roundtables.

Thanks everyone. That concludes our event. Have a great day.

Brian O'Mahony, Irish Haemophilia Society Ltd. - Chief Executive

Okay, thank you.
