2016 RNAi Roundtable: ALN-AS1 for the Treatment of Acute Hepatic Porphyrias Call

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- Ariel Lager, - Patient with AIP
- Bill Querbes, Alnylam Pharmaceuticals, Inc. - Associate Director of Research

PRESENTATION

Operator

Thank you, ladies and gentlemen, for joining today's RNAi Roundtable. We will be conducting two web-based question-and-answer sessions during the webcast.

(Operator Instructions)

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 of IR and Corporate Communications

Thank you. Good morning, everyone. Thanks for joining us for this RNAi roundtable. Today we will be discussing our progress with ALN-AS1 in development for the treatment of acute hepatic porphyrias.

I'm Josh Brodsky, Associate Director of Investor Relations and Corporate Communications at Alnylam. And with me today are John Maraganore, our CEO; Herb Bonkovsky of the Wake Forest University School of Medicine; Ariel Lager, a patient living with of acute intermittent porphyria; and Bill Querbes, Associate Director of Research at Alnylam.

Before I turn the call over to John, I just want to make a few comments. Today's RNAi Roundtable focused on porphyria is part of a series of roundtables that we have been hosting this summer, and which will go into the early fall. Today's event will end at around 12.45 PM Eastern time.

John will moderate two Q&A sessions during the roundtable. The first with Dr. Bonkovsky and Ms. Lager and then another with Bill at the conclusion of their presentation. If you would like to submit a question you can do so at any time during the event by clicking the ask a question button located 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 with that I will turn the call over to John.

John Maraganore, Alnylam Pharmaceuticals, Inc. - CEO

Thanks, Josh, and good morning, everyone. We are very excited to host today's RNAi roundtable on our ALN-AS1 program for the treatment of acute hepatic porphyria, where we believe there is an opportunity to bring a potential transformative therapy to patients in a disease with enormous unmet need.

Before we dive into the program, I would like to provide some overall context to Alnylam's effort. As you know, Alnylam is advancing RNAi therapeutics as a whole new class of innovative medicine. Largely through Alnylam's efforts, RNAi is now a clinically validated approach for the development of new medicines.

Alnylam's pipeline is focused on three strategic therapeutic areas, or STArs, including genetic medicine, cardiometabolic disease, and hepatic infectious disease. Today we have 10 programs in active clinical development, including two in Phase 3 trials. By the end of this year we will have 11 clinical stage programs and we will be advancing our hemophilia program into a Phase 3 study in early 2017. We expect to advance ALN-AS1 into Phase 3 later in 2017.

Our focus this morning is on ALN-AS1 -- again, an RNAi therapeutic for the treatment of acute hepatic porphyria. We are fortunate to have Dr. Herbert Bonkovsky with us today to provide a disease overview. We're also very fortunate to have Ms. Ariel Lager with us today to provide the important patient perspective.

So, with that, let me now turn the call over to Dr. Bonkovsky. Herbert?

Herbert Bonkovsky, Wake Forest University School of Medicine - Professor of Gastroenterology and Scientific Advisory Board Member of the American Porphyria Foundation

Good morning, everyone. I'm going to try to give a brief overview and summary about acute porphyrias. If I could have the second slide or slide number 12, these are disorders of normal porphyrin and heme synthesis. They are mostly acquired inherited, but there are some acquired forms, although we're not going to have time to talk about them today.

However, in addition to the inheritance, there are important effects of drugs, nutrition, alcohol and probably other genetic variations -- that is, genetic changes outside of the heme synthetic pathway. The major clinical features of the porphyrias are acute neural visceral attacks, that Ariel will tell us about, or cutaneous photosensitivity, sometimes both. In the case of two of the acute porphyrias, namely hereditary coproporphyria and variegate porphyria, there may be both of these manifestations.

But, by far the most important manifestations in these acute porphyrias are the acute attacks and sometimes, unfortunately, the

chronic neurovisceral symptoms and neuropathic pain that may occur. The symptoms, we think, are mainly due to the effects of ALA in the case of these neurovisceral attacks, or porphyrins in the case of the cutaneous manifestations.

The most common forms and the most severe form of the acute porphyria certainly is acute intermittent porphyria, AIP. The other common forms that we don't have time to talk about, they are mainly cutaneous porphyrias, PCT and EPP.

The next slide, number 13, this is the obligatory pathway of heme synthesis. I won't dwell on it, but note that the first in rate-controlling enzyme in this entire pathway is that catalyzed by hepatic ALA synthase. It condenses glycine and succinyl CoA to form this first committed intermediate ALA. Then the next step is two molecules of ALA forming a molecule of porphobilinogen, which is the first pyrrole in the pathway followed by a series of further enzyme reactions.

Notice that the diseases we are going to talk about today are diseases of the second enzyme in the pathway, ALA deficiency porphyria, the third enzyme porphobilinogen deaminase, said sometimes called hydroxymethylbilane synthase because it catalyzes the formation of a tetrapyrrole called hydroxymethylbilane.

And then on down to coproporphyrinogen and protoporphyrinogen. And in the final step in the pathway, the enzyme ferrochelatase inserts iron into protoporphyrin to form the end product, heme.

The next slide -- as I have already said, the classification usually is into the hepatic porphyrias, of which there are four inducible or acute forms -- ALADP, AIP, HCP and VP -- and chronic hepatic porphyrias -- porphyria cutanea tarda and HEP, hepatoerythropoietic porphyria We don't have time to talk about the those or about the erythropoietic porphyrias today.

The next slide -- the acute porphyrias have as major features attacks of neurovisceral pain and dysfunction; whereas, in the cutaneous porphyrias, there are blisters that may be severe, sometimes early onset, especially in congenital erythropoieticporphyria, also called Gunther's disease.

The next slide -- this is a summary, again, of the pathway. On the left is shown succinyl CoA plus glycine forming ALA, and then the pathway, shown horizontally. And notice the various sites of defects, ALA dehydratase, porphobilinogen deaminase, and the over-production and over-excretion of the precursors of heme in the pathway depending upon the specific enzymatic defects.

The other important point of this slide is that heme, the end product, has a negative feedback on the first and rate-controlling step, namely that catalyzed by ALA synthase. And in the next slide, number 17, is shown some of this regulation, which is actually quite complex.

Here, again, on the left you can see succinyl CoA glycine forming ALA/PBG eventually heme. The main user of heme in the hepatocyte is actually the family of enzymes, proteins called cytochromes P450, as shown by this heavy arrow int he slide.

Anything that breaks down P450, such as certain chemicals that are suicide substrates of P450s, or other things that induce P450s will tend to deplete the so-called regulatory heme pool and decrease the negative feedback regulation on ALA synthase, which is exerted at a number of sites, particularly, as shown on the slide, heme has the effect to increase the degradation of the message for ALA synthase. It also blocks the uptake of the pre-enzyme into the mitochondria where the enzyme is, in fact, active. A few years ago we also showed that heme within mitochondria enhances the breakdown of the enzyme within mitochondria.

The bottom line is that, through a variety of regulatory mechanisms, heme decreases the activity of hepatic ALA synthase. Contrariwise, when there is deficiency of heme there is an up regulation, which may be an uncontrolled up regulation leading to massive over-production of ALA and PBG, especially in the presence of distal defects in the pathway. And it is this increase in ALA that we now think leads to the major symptoms and signs of porphyria.

The next slide is just to give a brief summary of the enzymes involved in the four different acute porphyrias. As you can see, with the exception of ALA deficiency porphyria, they are all autosomal dominant, which means that you need only one dose of the abnormal gene in order to develop symptoms. However, it's also -- the next slide -- now known that probably -- I think, in fact, undoubtedly -- the prevalence of the genetic defects, as shown on this slide, are actually much higher than the prevalence of clinical disease, so that incomplete penetrance is the rule.

In fact, the latest evidence indicates that the actual prevalence of genetic defects that may give rise to the acute prophyrias are probably as high as about 65 per 100,000. And yet, as you can see here, even in Sweden where the disease is most prevalent, it is present in only estimated 8 to 10, and in the USA and in most other countries only 2 to 5 per 100,000. So incomplete penetrance and the presence of other factors -- genetic factors, nutritional factors, drugs -- are very important.

Next slide. The major clinical features are due to dysfunction or death of neurons with overlapping syndromes. We will hear about acute attacks, but also about chronic pain and paresthesias. And seizures are a particularly knotty problem because most of the seizure medicines are strongly contraindicated because they are inducer of cytochrome P450 and deplete the regulatory heme pool.

The next slide shows the symptoms in patients sick enough to need hospitalization. As you can, almost 100% have severe abdominal pain, about 60% various paresthesias, numbness, tingling. Constipation is common. Nausea and vomiting is common. And when that occurs, as it usually does, it makes the disease worse because nutrition and maintenance of nutrition is very important to downregulate ALA synthase.

The next slide shows the signs. And you can see that tachycardia is present in about 80%, dark urine in nearly that same percentage, and on down the list. Hypertension present in about 40%, may be quite severe during acute attacks. And so on.

The next slide again just emphasizes the precipitating or aggravating factors, especially excess alcohol, estrogens, hydantoins, things used for treating seizures, barbiturates, and the like. In fact, any inducer of hepatic cytochrome P450, which usually also are inducers of ALA synthase directly, are relatively contraindicated with patients of any of the acute porphyrias.

Unfortunately, some women have monthly attacks during the luteal phase of their menstrual cycles. People who are pregnant and particularly in the postpartum period, tend to have more symptoms. And, as I already mentioned, fasting starvation. And, in fact, now in the age of gastric bypass surgery, we had several patients who first developed symptoms after they underwent gastric bypass for obesity.

The next slide just gives a brief summary of the laboratory features during the acute attacks, which tend to be relatively nonspecific, except for the hyponatremia, which may be quite marked and severe and can be a tipoff to the right diagnosis. And, of course, urinary ALA, PBG and uroprophyrin are markedly increase. But you have to think about that in order to ask for the test and

make the diagnosis.

The next slide is the emphasis about who you should consider this disease in. So, in all adults, but especially in women in their childbearing years with recurrent abdominal pain, muscle weakness, hyponatremia, dark or reddish urine. And most patients, in my experience, if you asked them, will say that their urine turns dark or reddish, but it's often not recognized because nobody asked the question.

The diagnosis can be established rapidly with a qualitative test for PBG, which we used to have available, but we no longer have, generally. Most labs no longer run the Watson Schwartz test or the Hoesch test. And the Thermo Scientific kit has been taken off the market. So, this is actually quite an unmet need that we have for more rapid diagnosis.

The next slide shows one way of establishing a presumptive diagnosis, not a particularly fast way. Some patients' urine, as you see on the left side of this slide, even that urine just freshly passed look sort of reddish. If you leave it out exposed to light and air for about 18 to 24 hours, it sometimes turns black due to the formation of porphobilin and is a way of making the diagnosis.

The next slide shows the Hoesch test, which is very simple to do, actually. You start with Ehrlich's reagent, you add a couple drops of urine, and if you get an immediate red color at the top of that column of Ehrlich's reagent, it's a positive test. But, as I said, it is no longer being offered in most clinical laboratories, only reference lavatories.

In terms of the management, of course, primum nil nocere -- first, do no harm. So, avoid offending drugs and chemicals. Maintain nutrition. Watch for hyponatremia and magnesemia and correct it.

We recommend at least 300 grams of dextrose per day because there is also a glucose effect to downregulate hepatic ALA synthase. For pain, fortunately, the narcotic analgesics are safe. And we have safe drugs for hypertension tachycardia and the like, as shown.

The next slide shows the treatment of choice, which currently is intravenous heme. And this was actually the first patient that we ever treated back in 1970 with intravenous heme. And you can see the dramatic downregulatory effect on, in this case, plasma, ALA and PBG.

The patient was in renal failure and had no urine output. And after that first dose, we then gave a course of heme with a gradual a sustained decrease, particularly in PBG and the plasma.

The next slide shows some of the problems with heme therapy. It tends to be quite irritating to veins, it can lower the platelet count, it inactivates clotting factors. These effects can be minimized by giving heme as a heme albumin complex, which we generally recommend. And some patients require weekly prophylactic infusions.

Chronic heme can lead to secondary iron overload. We've also had patients begin to complain of headaches, myalgias, and apparently tachyphylaxis that may occur.

So, clearly a major unmet need is an alternative additional therapy. And as we shall hear momentarily from Bill, RNAi technology is showing great promise in this.

The next slide talks a little bit about prophylaxis. Obviously avoid the porphyrogen drugs, avoid prolonged fasting or crash dieting. Prompt and appropriate treatment of intercurrent infections. LHRH analogs for women with frequent cyclical attacks related to their menstrual cycles can be very helpful to them, although long term there is concern because they induce a medical menopause with hot flashes and tend towards osteopenia, osteoporosis. I've already talked about the periodic infusions.

The next slide shows some of the long-term risks. Mainly there is a marked increased risk of the development of hepatocellular carcinoma in patients with acute porphyrias. If you look at the bottom row, you can see that the odds ratio for men is 19. The odds ratio for women over 110 times increased risk of developing hepatocellular carcinoma, even in the absence of cirrhosis.

Cirrhosis is also more common in the acute porphyrias, probably related mainly to adverse long-term effects of excess ALA, although some of these patients have developed secondary iron overload due to all the heme that they have received.

Next slide, liver transplant is, in fact, a cure for acute intermittent porphyria. This was the first patient so are treated in the UK. And you can see there was a prompt and sustained decrease to normal in ALA and PBG, and no attacks in eight years after 37 attacks over 29 months prior to transplant.

The next slide is a summary of that experience, so far been performed mainly in Europe. I'm aware of two cases done in the US, both of whom were cured and have done well. There is an increased risk of development of hepatic artery thrombosis and so we recommend anticoagulation after liver transplant in these patients.

The next slide, then, is the summary. Acute hepatic porphyrias are a worldwide, pan-ethnic problem. The penetrance is low but it is devastating in a minority of patients, mostly women, with recurrent and severe attacks.

The key feature is uncontrolled induction of hepatic ALA synthase 1. And, as you will hear, RNAi therapeutic targeting has been demonstrated and a new therapy, especially self administration early in attacks, or a better prophylactic option for patients with recurrent attacks to treat themselves early at home, is a major unmet need and would represent a major advance in this field.

We are involved in the Porphyrias Consortium, a group of six centers. The next slide shows the principal investigators of that Consortium.

In the last slide, I will leave you with what was discovered when the Sistine Chapel ceiling was cleaned a few years ago. Between the finger of God and the finger of Adam is this primordial molecule of heme.

And I thank you very much for your attention.

John Maraganore, Alnylam Pharmaceuticals, Inc. - CEO

Thank you, Herb. That was a wonderful overview -- and interesting art history finding. I did not realize that. That's good to know. Why don't we go on to Ariel Lager who can bring the patient perspective to this discussion. Aerial, take it away.

Ariel Lager, - Patient with AIP

Thank you some much. And thank you for the opportunity to be here and to speak to the group. Thank you Dr. Bonkovsky. I was quite sure that when you alluded to the artwork found just below the surface of the Sistine Chapel you were, in fact, referring to the photograph of the Porphyrias Consortium Physicians. Quite a work of art.

But I do appreciate the opportunity to be here and to talk to the group. You've heard a bit about porphyria from a molecular and biological and medical perspective. And certainly you'll hear quite a bit from a research and treatment perspective, but hopefully I'm here to provide a little bit of a human perspective.

I'm a little bit intimately familiar with porphyria, although I may not understand a lot of the words that Dr. Bonkovsky used to describe the metabolic pathways and how works, and why it works. I just know what happens when it works. Unfortunately, I've experienced that firsthand, and tragically over the course of several years. So, I will tell you the human perspective and my story, which begins back in 2010.

I was 30 years old. I was working for an energy consulting company. I was working to build up the renewable business practice and serving as the in-house counsel there. I had a young daughter and we were in the process of adopting a second child. We moved out to the suburbs, we did all the things that people do when they begin to plan for their lives.

And then I tripped and I fell on my face, both literally and metaphorically. I fell and broke my nose. And the recommended treatment for the shattered septum that I suffered was surgery, a septoplasty to rebuild a part of my nose.

When the doctors tell you when you go into surgery that there are certain unexpected complications that happen in a tiny segment of the population, they don't even mention the latent metabolic disorder that you may have, and have lived with for 30 years, unbeknownst to yourself. The recovery from my surgery was very difficult and we couldn't figure out why.

After the physical recovery from the surgery itself had begun, I started to develop what we assumed was a raging infection because I developed a high fever, hypertension, high blood pressure. And then the pain came. I developed this abdominal pain that literally knocked me out. On more than one occasion I blacked out from the pain. I was vomiting interactively.

I was admitted to the emergency room and kept in hospital for several days at a time. And this cycle repeated itself. I would develope these tremendous symptoms of pain and peripheral neuroapathy and dangerously high blood pressure and tachycardic episodes. And I would be unable to keep down food. I would suffer from psychotic episodes and hallucinations and loss of feeling in my limbs, and just blinding terrible unresolvable pain.

And I would be hospitalized for a couple of weeks and they would give me pain medications and they would feed me through tubes and then I would gradually get better and go back to my normal life. And then in a month, six weeks later the same thing would happen again. The cycle went on for about six months.

I was one of the lucky ones. I got a relatively early diagnosis. I received my diagnosis within about six months of my initial attack. And when I received that diagnosis I had never heard of porphyria. I didn't know what the word meant. I learned from those experiences and from my medical experiences since really what rare disease means and what it means to your life, your health, your family, your loved ones and your ability to exist in the world.

Since then, it's been a journey to develop coping mechanisms, to develop a network of support, my family and friends, my physicians and the researchers who are working diligently to find better alternative treatments. I have been periodically unable to shake my recurrent attacks. I am on GnRH agonist therapy, which is medically induced menopause. I understand that it is not safe long-term or at least the results of it are unknown and untested over the long term.

I also was put on a regimen of weekly Panhematin intravenously. That's escalated up. Originally it was once a month and then it was once every two weeks and then it was once every ten days. And now it's once a week.

It doesn't prevent my attacks. I still get attacks, I still do have residual symptoms. But at least it's a way of managing my care in some way that doesn't involve spending most of my time in the hospital, and it's kept me alive this long.

So, I have been fortunate in the sense that, first of all, I did receive an early diagnosis. I have had access to the Panhematin and the treatment. And we will also talk a little bit about some of the downsides of that. But also I've been really blessed to not have some of the problems that my friends in the porphyria community have suffered with, which is recurrent seizures, partial or complete paralysis and death.

So, I do consider myself to be lucky to have what a lot of people might not consider a well-managed lifestyle of care, but I watch really closely my diet and exercise regimen. I try to control stress to the best of my ability. I don't take alcohol or take unsafe drugs all. But I do still need treatment to avoid acute attacks.

And even Panhematin as a treatment is not 100% effective. It is largely a timing game and the administrations of it are not a lot of fun, and not particularly convenient. You can see from some of the pictures on the first slide that I am on my second port now. The Panhematin has pretty much burned through my peripheral veins.

I do experience neuropathy in between attacks, but mostly I live in fear of acute attacks because they are debilitating and they are life-threatening. And they come with a whole host of medical and long-term problems, including, as Dr. Bonkovsky mentioned, an increased incidence of liver cancers and hepatic problems, as well as neuropathic issues, as well as overall decrease in my overall quality of life.

You can see on the next slide a little bit of discussion about the attacks themselves, which are not only life-threatening and debilitating but they are also terribly frightening. They're unpredictable and impossible to manage, even if you do take the best possible care of yourself as a patient. It isn't a guarantee to avoid the long-term potential damage of nerve damage, hormonal and bone density damage and cardiac risk associated with the long-term use of Lupron, as well as I have problems keeping on weight because when I get sick I have a nasty habit of vomiting unattractively for weeks at a time, which is not really good for maintaining a weight or a lifestyle or a family with children.

I also suffer just unbearable pain during my acute attacks and sometimes in between. And I realize long term, as my last [phys] indicated, that I am starting to show some of the signs after prolonged use of hematin, of increased iron levels and what I refer to as systemic inflammation, which leaves me prone to all other kinds of medical maladies and inconveniences.

It really is sort of a terrible awful disease. I don't purport to speak for certainly the rare disease community at all, and not for the other patients of porphyria, many of who have been dealt much more difficult life circumstances and difficulties in treatments than I,

but it's certainly a challenge, a devastating and difficult challenge, and a tremendous obstacle to living a normal life.

I do have those kinds of hopes long term that a treatment that is available, easy to administer, doesn't have long-term and short-term side effects, and actually works as a preventative prophylactic to these acute attacks would be a lifesaving treatment and a life-affirming treatment. The disease itself is a long-term struggle and it's also a moment to moment struggle.

So, we are excited about some of the research that we've seen. We are excited about the progress that science and pharmaceuticals are making. And we are optimistic about some of the research and where it's going to take us in the future. But mostly we are just looking to get our lives back.

I do appreciate your attention and listening to me prattle on about my life and experiences. And I welcome your questions and woudl be happy to answer any questions or continue any discussion anybody may have.

QUESTIONS AND ANSWERS

Answer – John Maraganore: Thank you. Thanks Ariel. Obviously thank you for sharing your personal experience. It really obviously inspires us to continue to work hard to bring this important medicine forward.

Let's now go into our first Q&A with Ariel and Herb. Let me start maybe, Ariel, with you. Obviously you talked very vividly about your experience. What has this meant for your family? And how has it impacted your family more broadly?

Answer – Ariel Lager: I'll tell you, it's the most difficult part of it to talk about, because my family and certainly my friends in the medical community have been a tremendous support to make. But I realize that my disease doesn't just impact me. Every time I am hospitalized, and to a lesser extent every time I am sick or receive a treatment, it cost me hours, days, weeks.

It's an impact to my overall life. It impacts the way that I'm able to or whether I'm able to do my job. But also it's a tremendous direct impact to my husband and my children, who have just been real troopers.

But it's a very difficult thing to live with, whether you are the patient or whether you're a caregiver, as my husband has become to me largely, with a disease like acute intermittent porphyria. And I worry tremendously about the impact that it has on my children. I have two small daughters. I worry tremendously about the likelihood that I have passed on that gene.

Acute intermittent porphyria is a metabolic disorder It's a genetic defect and it does come with a 50% chance that I will pass it on to my children genetically. And I worry about the kind of life that they'll have if they are cursed with a particularly active or overt demonstration of the disease.

My day-to-day life has really been and become a dancer around trying to manage my symptoms and trying to live within the confines or operate around this disease. It's very difficult for me to make plans, even short-term plans, to say I'd love to do something this Saturday, or my kids have a recital or I have a business meeting at work. All of those things are very difficult because I don't know when or if an acute attack is going to strike and I won't be able to live my life the way that I want to.

But it's also really difficult to plan in the long term because I don't know if I will have the physical or the mental facilities, or whether my survivability on the long-term horizon is very good under my current circumstances. So, the impacts to my family have been tremendous. The impacts to my job have been tremendous. And I think sometimes that it may be the only folks who have it worse in this disease than the patients are the family who suffers through with them.

Answer – John Maraganore: That's moving. One more question for you, Ariel, from the webinar. How many attacks do you have a year, if you are open to sharing that?

Answer – Ariel Lager: I am open to sharing. Thank you. It's a great question. I am one of those fun unusual patients who have recurring attacks of high frequency that we don't know the cause of. And we've tried to adjust for just about every trigger and I still experience just really frequent attacks.

In the most recent clinical trial that I participated in, in a three-month run in that we gauged I experienced nine attacks. In the course of an average year I can be hospitalized anywhere between 2 and 8 or 10 times. Those hospitalizations can last anywhere between a day and a week, sometimes longer. And in between I am on a prophylactic regimen of heme fusions.

It's pretty time consuming to manage my disease, as you might imagine. My attacks are extremely frequent. My hospitalizations have been very frequent, as well. So, it is a frequent problem, and it's not something that we've been able to manage or resolve through any conventional or even creative mechanisms.

But I do now receive the heme treatments. I've been doing this once a week for a while now. I've received hundreds in the last couple of years and I've been hospitalized dozens of times.

Answer – John Maraganore: Okay. Thank you Ariel. Thank you for sharing that perspective.

We have some questions here for you, Herb. One quick one is why is the Hoesch test no longer being offered? Is there a reason for that?

Answer – Herbert Bonkovsky: It really has to do with hospitals not being adequately reimbursed, and with all of the CLIA regulations and so on. And they are not doing it often enough, so maintaining a high degree of competencve.

The bottom line is that they've farmed all this out now to a few reference laboratories. And the big problem with that is that somebody comes into the emergency room with severe abdominal pain, maybe the doctor thinks could this be porphyria, especially if it's a young woman who has been a frequent flyer, recurrent needs for visits to the emergency department, and gets a screening urin for porphobilinogen. Unfortunately it takes at least three days, maybe five days or seven days, to get the result back. By then people have forgotten all about it and it gets lost in the shuffle.

Another problem is that, unfortunately, we as doctors don't know which test to order. And it's all too common in that setting for the doctor to order urine porphyrins not porphobilinogen. The urine porphyrins are usually actually elevated in acute porphyric attacks, but they are not diagnostic. There are lots of things that lead to elevations in urine porphyrins other than acute porphyric attacks.

So, it's just a real practical problem. And, as I say, there was this kit test that was being offered by Thermo Scientific for a while but

they dropped it because of lack of sufficient interest. So, we are now left without any rapid test for urine porphobilinogen.

Answer – John Maraganore: Thank you. Obviously these are things that, as new therapies emerge, perhaps things will improve on that front, as well.

We have another question here for you, actually, from a couple of people on the call. A lot of interest in understanding what are the potential on target effects of lowering ALAS1. In other words, are there expected toxicities that might be predicted based on the pathway or other medical information. Herb, if you could comment on that question.

Answer – Herbert Bonkovsky: Probably the biggest concern is that there might be too much of a decrease, leading to a critical deficiency of heme. It is an essential enzyme for normal heme synthesis and if you shut it off entirely it would be incompatible with life.

I think that concern has been somewhat allayed already in the early Phase 1/Phase 2 data, which Bill Querbes is going to go over in more detail. But, interestingly enough, it was a bit of a surprise, to at least me and I think others in the field, even the highest dose of the antisense to down-regulate hepatic ALA synthase 1 has not led to decreases below the normal, what might be called, just baseline level of activity of this enzyme. So, that is extremely exciting.

Obviously it is still early, and might there be long-term adverse effects chronic and ongoing down-regulation remains to be seen. My reading of what has been presented so far, mainly by Bill, is that we haven't seen evidence of any serious toxicities from the antisense. So, I'm extremely excited by these early results. The concerns about excess decrease in heme levels have not been borne out.

I think the other thing to keep in mind is that heme could be used with the antisense. They work by different mechanisms. And if in future there seemed to be a deficiency of heme, there is no reason why the heme couldn't continue to be given as is felt to be needed.

Answer – John Maraganore: That's helpful. You mentioned Bill several times and I think maybe it would make sense to transition to Bill to go over those data. And he can also highlight, I think, some of our data of this topic, as well. So, why don't we go ahead, Bill, and jump over to you.

Thank you, Herb. And thanks, Ariel. If you guys are able to stay on, then there may be questions for you with the second Q&A session.

Answer – Bill Querbes: Great, thanks, John. And thanks to Herb and Ariel for such a nice introduction to the disease.

I can jump right into an old review of our ALN-AS1 program. Slide 45 gives you overview of the heme biosynthesis pathway and our therapeutic hypothesis. As Dr. Bonkovsky pointed out, ALS1 induction in patients due to a variety of different attack triggers drives this over-production of toxic heme intermediates, ALA and PBG, in the case of AIP, or acute intermittent porphyria, due to a deficiency in the PBGD enzyme, which causes this pathway bottleneck and the accumulation of these intermediates.

ALN-AS1 utilizes our GalNAc conjugate technology with ESC chemistry. It's administered subcutaneously. Our therapeutic hypotheses is that one thing the upregulation of ALA1 with ALN-AS1 should be sufficient in order to prevent this overproduction of these heme intermediates, ALA and PBG, and prevent attacks from occurring.

One of the beautiful parts of this approach is that by targeting ALAS1, which is upstream of the genetic defects in all of the hepatic porphyrias, it should work for all of these diseases. So, AIP, variegate porphyria and hereditary coproporphyria.

Slide 46 highlights two potential uses for ALN-AS1. It's important to note that the primary indication for ALN-AS1 is for prophylaxis in these patients with recurrent attacks, which is clearly, as Arial nicely highlighted, the highest area of unmet need. But there's also opportunities potentially for acute treatment of attacks.

In the recurrent attack patients, they have these cyclical periods of ALAS1 upregulation. With ALN-AS1 prophylaxis, mild chronic suppression of ALAS1 for preventing induction and bringing values into normal range should lead to reduction in acute attacks, reduce the need for heme and reductions in hospitalizations. And in frequent, monthly or quarterly subcutaneous injection of ALN-AS1, could really be quite transformative for these patients.

Additionally, there are likely opportunities down the road if our onset of action is rapid, where it could rapidly dive down ALAS1 levels that are induced during an acute attack, to lead to rapid improvement in symptoms.

Slide 47 speaks to existing data in the literature that gives us confidence that targeting ALAS1 specifically within liver and reducing ALA and PBG will impact attacks. The first piece of data is we know that heme works and somewhat pharmacologically validates the target by working through pathway feedbacks to downregulate ALAS1. If you give liver cells encultured heme, ALAS1 is rapidly downregulated.

The other important pieces of data out there is liver transplant experience. As Herb mentioned, liver transplants have been shown to be curative. Additionally, domino transplants, where you take a liver from an AIP patient and give that to another recipient, this leads to an increase in ALA/PBG and attack-like symptoms.

So, we think cumulatively these liver transplant data suggest that the toxic CCs are coming specifically from liver, and shutting off the production in liver should be sufficient for therapeutic benefit.

Additional evidence on the toxicity of ALA and PBG, and most likely ALA, one example is a patient who with an HTC tumor that spontaneously produced ALA and PBG, resulting in similar symptoms to AIP, that resolved with tumor resection, and in lead poisoning, where lead inhibits the second enzyme in the pathway leading to ALA upregulation, and some similar symptoms to AIP.

These are additional examples that point to the toxicity of ALA. And, again, if we can turn off production in liver we should see some clinical benefit.

Slide 48, now moving towards our Phase 1 study, describes the two patient populations that were utilized. The first group are what we call asymptomatic high-excreter patients, also referred to as ASHE. These are patients that secrete high levels or intermediate levels of key attack biomarkers ALA and PBG.

One of the challenges of running this study in a normal healthy population is you can't detect reasonable levels of these. This

population is also more stable since they are not experiencing attack symptoms for initial clinical studies focused on safety. This population has actually been utilized in prior enzyme replacement clinical trials before, the reference mentioned below.

The second population is the patient population with recurrent attacks, which is our go-forward intent-to-treat population with the highest unmet need for prophylaxis. Again, we would like to make sure that we identify the proper dosing regimen in this population before progressing to later-stage clinical development.

On slide 49 is an overview of our main Phase 1 study objectives. The study is composed of three parts -- Part A and B, which is a single ascending dose and multiple ascending dose design, or SAD/MAD, in ASHE patients; and a Part C, which is a multi-dose study in patients with recurrent attacks. The focus of today's talk is on the first two parts, where the primary objectives were safety and tolerability of ALN-AS1, and the secondary objectives were to characterize the PK and PD of ALN-AS1.

In addition to measuring ALA and PBG, we wanted to evaluate our cERD assay for monitoring targeted ALAS1 mRNA levels in circulation. More on that in a minute.

And in Part C, that we're not going to get into today, the main focus will be safety and biomarker changes in patients with recurrent attacks. But we will also be evaluating signs of clinical activity, including looking at reductions in attack frequency or severity of attacks, as well as heme treatment.

Slide 50 shows the key eligibility criteria for participation in this study. The study included patients 18 to 65 years of age with a confirmed diagnosis of AIP for sequencing for PBGD, also known as HMBS mutation. There was also a requirement for urinary PBG levels to be elevated greater than 4 millimoles per mole creatinine; hence, high excretion.

In Parts A and B we excluded patients with recent attack or heme use in the last six months or those utilizing new medications. And they must be stable on any medication for other conditions. In Part C the inclusion criteria was greater than or equal to two attacks in the last six months on study, or currently using heme prophylaxis but willing to discontinue for participation on study.

An overview of the cohorts in the study are on slide 51. There were five cohorts in Part A ranging in dose levels from 0.035 up to 2.5 mg per kg, that were randomized 3 to 1 in a single blind manner drug to placebo. In Part B of this study there were two cohorts that were randomized similarly 3 to 1 drug to placebo for cohort, but they received two monthly doses of drug at either 0.35 or 1 mg per kg. In Part C, currently ongoing, the patients were monitored in a run-in period to understand baseline disease activity, and randomized 3 to 1 in dose to drug. In this way we can compare the disease activity on drug to the observation period for each patient.

Slide 52 shows the demographic information for Parts A and B of the study. The population was primarily female, consistent with the expected gender ratio of this disease. And there were multiple AIP genotypes represented with the different mutations listed. All patients had significant elevation of ALA and PBG well above the upper limit of normal. The average levels were approximately 13-fold above normal levels of PBG and approximately 3-fold elevations of ALA compared to normal.

Turning to safety data from the study on slide 53, ALN-AS1 was generally well tolerated in Parts A and B of the study. Most importantly, there was no drug-related severe adverse events or discontinuations due to AEs. Of the three events listed, including two in the SAD and one in the MAD, they were deemed unrelated to study drug by the investigator.

78 total AEs were reported in the SAD and MAD, with 62 determined to be not related or unlikely related to study drug. All the AEs in Part A of the SAD portion of the study were mild or moderate in severity, with one exception noted above that 0.1 milligram per kilogram. Two injection site reactions were reported, but both were mild and transient.

All AEs, 29, in Part B of the MAD portion of the study, were also mild or moderate, with no injection site reactions reported. There were no clinically significant changes in vital signs, EKGs, clinical laboratory tests, or physical exam findings. So, in total, the ALN-AS1 safety was quite good overall.

Slide 54 gives an overview of our cERD essay. Unlike some of our other programs where the liver target is secreted protein measurable in blood, the ALAS1 protein is not a secreted protein. It created a challenge for how to directly monitor target gene, lowering non-invasively without a liver biopsy.

As a results, our scientists here at Alnylam took advantage of the fact that assays secrete high levels of exosomes which contain mRNAs and microRNAs that are secreted in the circulation. We found that we could reproducibly detect the ALAS1 mRNA in both blood and urine that was secreted from the liver.

On the right side of the graph shows proof of concept studies in nonhuman primates after dosing with ALN-AS1. In this case, levels of ALAS1 mRNA from a liver biopsy tightly correlated with the levels of ALAS1 measured in circulation. We have similar data showing that we can detect levels of ALAS1 in urine and in serum. We think that this is an incredibly powerful approach to monitor the PD of ALN-AS1, understand the kinetics of lowering, and understand the relationship of lowering ALAS1 and downstream changes in ALA and PBG. And we continue to use this in all of our clinical studies as well as our natural history study.

Turning to the PD results, slide 55 shows the ALAS1 mRNA study results, utilizing the cERD essay. On the left-hand side of the slide shows baseline levels of ASHE patients in Part A and B compared to levels shown in normal healthy volunteers not participating in the study. And, as expected, given the therapeutic hypothesis, ALAS1 mRNA levels were upregulated about threefold in patients compared to normal individuals.

On the right-hand side of the graph you can see robust dose-dependent lowering of the ALAS1 mRNA with a nadir achieved around day 21. The effects, however, are quite rapid at higher dose levels, with some reductions in ALAS1 mRNA detected within a couple of days at the highest dose of 2.5 milligrams per kilogram. And most of the groups at higher doses we see very sustained lowering of ALAS1 mRNA lasting beyond 42 days.

Importantly, we could lower ALAS1 mRNA levels from the induced level to near normal range. And this is shown with the dotted line on the graph at the right. Simply taking these patients from an upregulated level up to about threefold, and bringing them down to a normal range, you will begin to see on the next slide, slide 56, resulted in very dramatic dose-dependent lowering of ALA and PBG, even following a single dose.

On the left-hand side you can see the ALA data; on the right-hand side you can see the PBG data, the maximum knockdown of 86% and 95% of ALA and PBG, respectively, at the highest dose. ALA and PBG reductions could be detected within a couple days. And the long duration of effect we think supports monthly if not quarterly dosing moving forward with this drug.

Finally, in the tables on the inside of the graph is the values of ALA and PBG are expressed as a percentage of predose. What we can show in this table is that at the higher doses many of these patients are reaching normalization of the absolute levels of ALA and PBG. So, values have reached the upper limit of normal with these particular assays, which is incredibly exciting.

Slide 57 shows nice correlation graphs of the relationship between ALAS1 mRNA and ALA and PBG in the SAD portion of the study. The ALAS1 levels on the x-axis correlate extremely well with the reductions in ALA and PBG on the y-axis, showing this is a very tight relationship, with r-squared values of 0.79 and 0.87, respectively. And these correlations were also seen very nicely in all preclinical data in these model studies where he saw that about a 50% or 60% reduction of the ALAS1 mRNA resulted in up to 80% to 90% reductions in ALA and PBG. So, this is very consistently with what we saw preclinically, as well.

Slide 58 shows the ALAS1 mRNA changes in the MAD portion of the study. Following two monthly doses of ALN-AS1 at 1 milligram per kilogram, we could see up to 54% reduction in ALAS1 mRNA. The nadir was around day 21, with the effects being sustained out beyond 70 days.

While we see nice dose response of lowering we did not see additive effect with the second dose. The degree of maximal mRNA lowering was similar to the level seen following a single dose at those particular dose levels.

Slide 59 shows the ALA and PBG results from the MAD portion of the study. Again two monthly doses led to a very substantial decrease in ALA and PBG. Similar to the mRNA results, multiple doses did not appear additive and maximal levels of ALA and PBG lowering was similar to those after a single dose of 0.35 over 1 milligram per kilogram, including 84% reductions in ALA and 89% reductions and PBG.

And, again, at the higher dose of 1 milligram per kilogram we could detect very nice normalization of their absolute levels of ALA and PBG.

In summary, of the data presented to date, ALN-AS1 was well tolerated, both in the SAD and MAD portions of the study. There were no drug-related SAEs or discontinuations due to AEs, no dose-dependent AEs or clinically significant changes. We showed some nice validation of our cERD essay to monitor ALAS1 mRNA in a noninvasive manner. This assay really confirms the hypothesis that ALAS1 upregulation is a key driver of this increased ALA and PBG production in these patients.

Furthermore, a lowering of ALAS1 levels, about 50% to 60%, just from an induced level to the normal levels seen in normal healthy individuals, was sufficient to lead to the very robust lowering of ALA and PBG. And related to Herb's earlier point, I think this is a really reassuring thing from a safety perspective, that taking them from these induced levels to a normal range is sufficient to see very dramatic decreases in ALA and PBG.

The next steps for the program, for this study in particular, are continue to monitor recovery of patients in Part A and B, continue Part C in recurrent attack patients, with initial biomarker data to be presented at ASHE in December pending acceptance of the abstract. And assuming good results we plan to initiate a Phase 3 study in 2017.

Shifting gears slightly, one other thing we wanted to mention is we also continue to make great progress with our EXPLORE, our natural history study. This is an observational perspective, natural history study, of all of the acute hepatic porphyrias, including AIP, VP and HCP, where we're trying to better characterize the signs and symptoms of attacks, treatment practices and overall burden of disease.

We included in the study that patients were required to have had at least three or more attacks in the last year or currently be using prophylactic treatment, either heme or GnRH analogs, to prevent attacks. This is a six-month study with opportunity to continue beyond that ,which includes a couple of office visits at the start next month. And then there's a collection of urine and blood samples for biomarker analysis, and collection of a number of different questionnaires to capture the important symptoms and treatment information.

Slide 62 highlights some of the key objectives of this study that are important to mention. This includes characterizing all attacks, signs and symptoms, understanding event rates in this population, and different treatment practices. How are patients using heme and does this change in different countries. We also want to understand patient medical history, medication usage, and explore the use of potential biomarkers for future studies.

Finally, we also wanted to capture quality of life data and healthcare utilization data. As Ariel really nicely highlighted, we know that many of these patients than the large number of days per year in the hospital. So, we like to capture that type of information. And operationally there has been a ton of learning that will benefit us moving forward with this program.

So, we have completed enrollment of 112 hepatic porphyria patients in the study. We've good representation of patients both in the United dates and throughout the EU. We plan to present initial six-month data from all patients at ALS in November. The data from the study will be important to help perform the design of the pivotal study moving forward in 2017.

So, with that, we can conclude an overview of the program and we can move to the Q&A portion.

Answer – John Maraganore: Thanks Bill, thanks that's a great overview. Thanks for doing that. I have a few more questions and I think some of these are best answered by you, Bill. There may be a few here that would also be answered well by Herb.

Let's start with one for you in the Phase 1 study, levels were normalized in three of three patients at the higher dose group but PBG was only normalized into a three. Why is the BG hired to normalize and what is the significance of that potential expectations of a run clinical activity? Seatback the point there are both of these biomarkers are very highly elevated. Barely bring them down at or near normal levels is probably beneficial, so I think that's a key piece, . And I think from some of the data that we talked about I think both that Dr. Bonkovsky mentioned really thought that ALA is probably the main toxic I think we are more focused on one of the two metabolites would be more focused on transaminase ALA. That's perfect. Another question is whether or not we can predict or expect. And maybe ,Herb, you would have a, hereto. The level of mRNA reduction that's going to be needed to reduce the incidence and severity of acute attacks.

Answer – Bill Querbes: Yes I will give a few remarks and maybe Herb can, and also. I think from the preclinical data bringing animals from -- that are prophetic animals down from an induced level about 50% resulted in 80% to 90% reduction in ALA PBG. Start of the data is starting to see it was a correlation graph suggest a somewhat on where 50% to 6% lower from the induced Lowell into a normal range for ale and PBG and normalization want to normalize what we think are the toxic species we hope that will translate to clinical benefit.

Answer – John Maraganore: Okay ,Herb. Do you have any comments or any perspective on a question?

Answer – Herbert Bonkovsky: I can just comment that there are many patients with acute porphyrias particularly acute intermittent porphyria who are always over excreting and overproducing ALA and PBG, and yet they are not having acute attacks. So, why some patients can do this without having difficulty is an enduring mystery. That being said, the treatment does -- effective treatment definitely does decrease the mRNA for alias one -- ALAS1 as was shown very nicely inside 57, that there is virtually a linear relationship between the decrease in ALAS1 mRNA and decreases even Don to essentially normal in urinary ALA and PBG. So, I'm not sure that in the real world of treating patients and trying to improve their symptoms, it's going to always be necessary to bring the level of ALAS1 mRNA fully down to what is the normal range. It may will be that many patients will have a cessation of attacks while that level is still 1.5, two, 2.5 to three times what's considered the normal range. I think that remains to be obviously seen with much larger numbers of subjects and particularly with treatment now of patients who are experiencing acute attacks. But as I stressed earlier, I think the very exciting result is that even the highest dose of the Almylam S1 drug has not led to a decrease below the normal range for ALAS1 mRNA. That was my main concern of what might happen with this drug, and the fact that we haven't seen this and now a number of studies, admittedly still small numbers, but growing numbers of patients is extremely exciting, and reassuring about long-term safety and tolerability of this new approach.

Analyst: NEW SPEAKER

Question – NEW SPEAKER: Just had one more point to that I think in the absence of really knowing that answer we are taking the approach trying to lower ALA and PBG is much as possible but I think what Herb points out nicely is that merely blocking the cyclical up regulation events could also be sufficient in reality maybe we don't need to lower ALA.

Question – NEW SPEAKER: Yes, thanks another question that came in his around where do we go next? Assuming the recurrent attacks study is positive, encouraging, what does the phase three trial look like? And what level of attack reduction would be clinically meaningful? Maybe Bill you can take that maybe Herb you might have some perspective on that as well.

Question – NEW SPEAKER: Sure. I think we are going to gather the learnings from this is ongoing. Couple that with some of the data we are getting from our natural history study and continue to discuss with expert such as try to develop a pivotal study for next year. I think that probably looks like reductions in the number of attacks. Secondary endpoints that's part of things such as reductions in a lame PBG. Things such as hospitalization or urgent healthcare use. Those types of and points.

Question – NEW SPEAKER: I would consider more than a 30% decrease in the frequency of attacks or days in hospital to be both clinically and biologically significant. I think the other thing that we may will see is that people will no longer need weekly human fusions are less frequent human fusions and I think that will be a very useful secondary endpoint. Ariel I think pointed out so poignantly, the difficulties with chronic emus. The fact that her peripheral veins are just talk on. She requires central venous access through ports. The ports become clotted, they become infected, they are a pain to have to live with. So I am very hopeful, and I think in fact it is likely that we will see a decreased need for human fusions. I am treating patients with weekly. It is keeping them out of the hospital. It is a half a day per week that is shown by the time they get there, by the time the thing is given, and just as a half a day out of your life every week. Maybe Ariel she is still on million dollars, and more.

Question – NEW SPEAKER: Yes I'm here, thank you Brent Koski -- date Dr. Bonkovsky for settings light on a. The heme has pretty much burned through my peripheral veins at this point. Initially. You have to understand this is a rare condition, and certainly things like that. But I've also experienced severe problems with it being properly administered. I get really raging the bad headaches. And nausea every time. Every single time. Which is once we. So the problem with it. And I am loath to criticize and critique something that is keeping me alive. So I realize I'm depending on it to stay out of the hospital and stay alive but at the same time, the space in between, feeling crappy forgive my language is getting smaller and smaller because the side effects and the overlap of symptoms and the next round of recurrent symptoms when I need treatments are just getting closer and closer together. And all the while I am aware of just how damaging long-term the pen he mentioned treatments can be close to my veins into my overall system. Not to mention the told that the Lupron is taking. And it is a tremendous inconvenience. Further down the list of priorities staying live. And second is staying out of the hospital in the ICU. And then those long-term and permanent disabilities that so many of my friends and the perfect community have experienced. Paralysis and seizures on long-term health crises. But wait on the list is also the super inconvenience of having to have and fusions once a week, they can only be administered during infusion center hours or when the nurse can come out, which means that I have to miss time from work, and means I have to miss time otherwise that I would spend with my kids and they spend probably a day, day and a half after every treatment feeling lousy. So I appreciate that the treatments keep me alive, I really do, but it since me like there has to be a better way.

Question – NEW SPEAKER: Yes, okay Ariel, we agree. Herb, did you have a comment that?

Question – NEW SPEAKER: Ariel, how would you answer this question about how much of a decrease is meaningful important in terms of like an endpoint for a clinical trial. How much of a decrease in numbers of attacks four days in hospital? How would you answer the question?

Question – NEW SPEAKER: I don't know if we lost Ariel there.

Question – NEW SPEAKER: We must have.

Question – NEW SPEAKER: Okay. Look, it's a good question and would love to understand perspective on it. There is one more question I think we can ask quickly. Is it possible -- this is best for Herb. Is a possible there is a larger proportion of patients there with milder symptoms? Obviously the prevalence of the disease based on just the genetics when argue that it should be more prevalent. Is a possible there is more of a mild moderate clinical phenotype other in patients that are getting diagnosed but are living with some degree of pain? They could be addressed in the future? What to think Herb?

Question – NEW SPEAKER: I'm sure that probably most of the people in the US and for that matter around the world that actually have one of the acute porphyrias have never been diagnosed. They don't know they have it. Obviously if there is a family member, maybe the diagnosis has been made, although I have been amazed even among be family members of people that we know have porphyria, how relatively unusual it is that they are willing and interested in having genetic testing. They feel like I'm feeling okay so I don't want to know. But if I had this in my family, I would want to know for sure rather I am at risk or not. But more to your point, there certainly are patients with known porphyria or not having the severe problems that Ariel unfortunately has experienced, but who are having milder degrees of pain. They are treating themselves with high carbohydrates, with payments, with this that and the other thing. And if this drug were shown to be safe -- and of course affordable is going to be the next issue -- but I think that the universe of patients who might will turn out to benefit from this long-term downregulation of hepatic ALA synthase is probably far greater than we imagine at this moment. And I think the eventual market might be very substantially greater than the most severely affected ones where the ones that we been concentrating on this morning.

Question – NEW SPEAKER: That's our suspicion, as well. This income I want to thank you and Ariel if you can so Harris I want to thank you ,as well ,in particular.

Answer – Ariel Lager: I can I apologize. I briefly disconnected. But I do appreciate you having us on the call and I wanted to reaffirm Dr. Bonkovsky is -- that's my suspicion as well that just for my own experience the trouble of getting diagnosed in the understanding of this is an ultra- rare disorder I think is a self-fulfilling prophecy. I think doctors are hesitant to test for, I think patients are loath to acknowledge it. And I think it is probably under-reported, at least from my perspective.

Answer – John Maraganore: Thanks. I think we now have to close the call. Joshua had some final comments. Go ahead.

Answer – Josh Brodsky: Yes, I do, John. Thanks to all of our speakers and to everyone on the webcast for joining us today. A replay and slides of this event will be posted on the Alnylam website at Alnylam.com/roundtable. Follow shortly thereafter. You can visit that page to view bios of the speakers. We have two more roundtables in this 2016 series. We hope you can join us on Tuesday September 27 at 10.00 AM Eastern time as we discuss our ale and the for primary type 1. And our final event of the series on Tuesday October 11 focused on ALN-HDV program. For more details visit www.Alnylam.com/roundtable. This concludes today's event. Thanks ,everyone, and have a great day.

Answer – Operator: Have a great day, everybody.
