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EDITED TRANSCRIPT

ALNY - Alnylam Pharmaceuticals Inc RNAi Roundtable: ALN-ASI for the Treatment of Hepatic Porphyrias

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Josh Brodsky - Alnylam Pharmaceuticals, Inc. - Senior Manager IR and Corporate Communications

Good morning, everyone, and thank you for joining us for our RNAi Roundtable to discuss the progress we are making with ALN-AS1 for the treatment of acute hepatic porphyrias. I am Josh Brodsky, Senior Manager of Investor Relations and Corporate Communications at Alnylam. And with me today are John Maraganore, Chief Executive Officer; Dr. Robert Desnick of the Icahn School of Medicine at Mount Sinai Hospital; Desiree Lyon Howe of the American Porphyria Foundation; and Bill Querbes, Associate Director of Research at Alnylam.

I will be turning it over to John shortly, who will provide you with a brief introduction. But first, a few comments.

Today's RNAi Roundtable, focused on our ALN-AS1 program, is the eighth and final in our series of roundtables that we have hosted this July, August, and September. The event today will end at around 12:30 PM Eastern Time. We will have two Q&A sessions, and you may submit a question at any time during the webcast by clicking the Ask a Question button located above the slide window on 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. - Senior Manager IR and Corporate Communications

Good morning, everyone, and thank you for joining us for our RNAi Roundtable to discuss the progress we are making with ALN-AS1 for the treatment of acute hepatic porphyrias. I am Josh Brodsky, Senior Manager of Investor Relations and Corporate Communications at Alnylam. And with me today are John Maraganore, Chief Executive Officer; Dr. Robert Desnick of the Icahn School of Medicine at Mount Sinai Hospital; Desiree Lyon Howe of the American Porphyria Foundation; and Bill Querbes, Associate Director of Research at Alnylam.

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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 now turn it over to John.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Thanks, Josh. Welcome, everyone, to our final RNAi Roundtable discussion. Before we get started, I would like to provide some broader context.

Over the last several years, Alnylam has built what we believe to be a reproducible and modular platform for RNAi therapeutics as innovative medicines. In our efforts we are focused on liver-expressed, genetically-validated disease targets where, to date, we have demonstrated a 100% success rate in achieving robust target gene knockdown in every species -- most importantly, in man.

Indeed, with our seven programs today in the clinic, we have now presented results from six of those seven. And all six programs have demonstrated positive proof-of-concept in our human studies.
We also focus on programs where proof-of-concept can be demonstrated in the earliest phase of clinical development; and then, also, on indications where there is a definable path to approval and, very importantly, to market access for patients. ALN-AS1 is exactly such a program. This overall approach has resulted in a robust and growing pipeline of medicines across our three strategic therapeutic areas, which we call our STArs.

And as you can see on this slide, Alnylam currently has seven clinical RNAi therapeutic programs, including two in phase 3 trials. And by the end of this year, we will have nine clinical programs.

Of course today’s focus is on ALN-AS1, our investigational RNAi therapeutic targeting ALAS1 for the treatment of acute hepatic porphyrias. We are very pleased today to have Dr. Robert Desnick and Desiree Lyons (sic) with us today. Bob is a world-renowned authority in porphyria. Dee, of course, joins us in her capacity as the head of the American Porphyria Foundation.

It is a great pleasure to have both of them on the call today. They have wonderful perspectives and experience to share with all of you. So with that, I am now going to turn the call over to Dr. Desnick. Bob?

Robert Desnick - Icahn School of Medicine at Mount Sinai - Dean, Genetics and Genomic Medicine and Professor and Chair Emeritus, Department of Genetics and Genomic Sciences

Thank you, John. Good morning, everyone. I will provide some relevant background information on the acute hepatic porphyrias. Next slide.

Specifically, I will briefly discuss heme biosynthesis and this regulation, the biochemical basis of the porphyrias, their prevalence, the major clinical manifestations of the life-threatening acute attacks, and their current treatment. Next slide.

The porphyrias are inborn errors of heme biosynthesis. Here you see the heme biosynthetic pathway, which involves eight enzymatic steps in the conversion of glycine and succinyl CoA at the top through a series of intermediates to heme, as shown in red at the bottom. This is a very archaic pathway that has a very unique feature, which is feedback regulation.

Now, also shown here, you will see the deficient activity of one of four different enzymes in the pathway -- shown in blue -- that result in one of the acute hepatic porphyrias, which are indicated in the blue boxes. Note that the pathway is under negative feedback regulation. The red dotted line indicates this, meaning that when the level of free hepatic heme is low, it signals the induction of the first enzyme in the pathway, aminolevulinic acid synthase, or ALAS1 for short.

That increase increases heme synthesis. This signal increases the ALAS1 messenger RNA, which is the target of our efforts to treat these diseases. And once the message is increased, it results in increased ALAS1 enzyme activity and increased heme biosynthesis.

Now, in patients with each of the acute porphyrias shown in the blue boxes, the respective enzyme deficiency acts as a metabolic block. The common result when ALAS1 is induced is the accumulation of the toxic porphyrin precursors ALA and PBG, shown in green. So it is important to focus on ALAS1, its message induction. And in the porphyrias, the common block leads to the accumulation of ALA and PBG, which are toxic precursors in the plasma and urine that gain access and cause the symptoms. Next slide.

Of the four acute porphyrias, three -- acute intermittent porphyria, AIP; hereditary coproporphyria, HCP; and variegate porphyria, VP, are autosomal dominant diseases. And the fourth, ALA-dehydratase deficient porphyria, or ADP, is a very rare autosomal recessive disorder. The major clinical manifestation in patients with these diseases is the life-threatening acute neurologic attacks. Many patients also develop neuropathic pain and a progressive neuropathy.

The diagnosis is made biochemically during an attack by demonstrating markedly increased urinary or plasma ALA or PBG levels due to the markedly induced ALAS1 mRNA. Gene mutation analysis can identify all patients. Next slide.

The prevalence of the acute porphyrias has been estimated in several European countries and in the US to be about 2 to 5 symptomatic patients per 100,000 population. Sweden has a higher prevalence of about 1 in 10,000 to 20,000 patients per population due to a genetic founder effect.
The American Porphyria Foundation, the only porphyrias patient advocacy organization in the US, has over 8,700 members, of which about 3,000 have indicated they have acute porphyrias. Of these, 1,800 have been biochemically or mutation confirmed. Next slide.

During the past five years, our DNA diagnostic laboratory at Mount Sinai has mutation confirmed over 430 patients, acute intermittent porphyria or AIP being the most prevalent. We have genotyped an increasing number of patients over these years as awareness of these diseases has increased. It should be noted that many patients are initially misdiagnosed. Others remain undiagnosed. Typically, the diagnostic delay from first symptoms to diagnosis is about 10 years. Next slide.

The mechanism of pathogenesis of the acute attacks is depicted in this cartoon. In healthy individuals, hepatic heme biosynthesis is controlled by the level of free heme, even under conditions that trigger acute attacks in patients with the acute porphyrias. These attack triggers include the administration of certain drugs that are porphyrinogenic and induce certain P450 enzymes. The other causes are dieting or fasting and certain changes in hormone status in women.

In patients with the acute porphyrias, these triggers deplete heme and upregulate hepatic ALAS1 mRNA levels. But the specific enzymatic deficiencies in each of the acute porphyrias lead to the accumulation of toxic ALA and PBG and then to the acute attacks. Next slide.

Acute intermittent porphyria is the most common acute porphyria. And there are three groups of patients. Those who have recurrent attacks -- we define that as about 3 to 4 per year in both men and women. These attacks can be as frequent as weekly or monthly, and many women have monthly attacks during the luteal phase of their menstrual cycle, when progesterone levels increase.

Then there are those who have sporadic attacks; we define that as less than three per year, both men and women. And finally -- they're an important group -- those who are asymptomatic high ALA and PBG excreters. These men and women typically have had an attack in the past and continue to have persistently high levels of plasma and urinary ALA and PBG, presumably making them more susceptible to attacks. Next slide.

The acute porphyrias typically began with a prodrome of fatigue; confusion, often called brain fog by patients; insomnia; and other prodromal symptoms, which then progress to the excruciating abdominal pain, which is accompanied by nausea, vomiting, weakness, etc. These symptoms take the patient to the emergency room for treatment; and, if not treated, the symptoms can progress to life-threatening convulsions and paralysis. So this is really a very, very serious disease, particularly if unrecognized.

Let me give you a case study -- next slide. This is a patient of mine who has recurrent attacks. She is a 30-year-old professional woman who, in one year, had 20 acute attacks and 32 years (sic - days, see slide 19) of treatment, which was intravenous heme infusions. Currently we put her on weekly prophylactic heme infusions. But she still has breakthrough attacks, indicating that the treatment is not really as effective as we would like.

Now, the management of the acute attacks is by admission to the hospital or an outpatient clinic for heme infusions. Any known precipitant is withdrawn. Opiates are administered for pain and chlorpromazine for nausea, and intravenous glucose may be administered. And as soon as possible, the hematin infusions are begun. Next slide.

Intravenous hematin is administered to correct the low hepatic heme level to decrease the elevated ALAS1 mRNA and the toxic ALA and PBG levels. An initial dose is 3 milligrams to 4 milligrams per kilogram daily for four days, but most patients are treated until symptoms are gone in the hospital. Intravenous glucose is appropriate only for very, very mild attacks or until hematin is available, as many hospital pharmacies must order the drug. Next slide.

Hematin was the first orphan drug approved by the FDA in 1982 based on small, open-label studies. It has been in clinical use for over 30 years. It has some adverse reactions or side effects, including phlebitis, coagulopathies, and others listed here. Tachycardia can occur in patients on long-term treatment.

Many patients use ports for administration, which can lead to infection and, recently, to frequent replacement due to clotting. Chronic use can also lead to iron overload, because iron is a part of the hematin material. Of note, the FDA has not approved hematin for prophylactic use. Next slide.
Another kind of heroic approach used in the most severe cases is liver transplantation. The first case was in a 19-year-old Englishwoman who had recurrent neurologic attacks -- over 37 in 29 months. She was unresponsive to the hematin treatment. After transplantation, there have been no attacks now for over eight years.

This and subsequent liver transplants proved the pathologic importance of the liver in these disorders. In fact, domino transplants of the explanted AIP liver into patients who would not receive a liver transplant but had liver failure resulted in the recipient of the AIP liver developing AIP, with increased ALA and PBG and acute attacks. However, we should point out that liver transplantation has been limited to the most severe cases -- there are about 20 accomplished in the world today -- due to the morbidity and mortality associated with transplantation. Next slide.

Based on experience with AAV gene therapy and the AIP mouse model in my laboratory and in Spain, Unicure has completed a phase 1 clinical trial in eight patients who have recurrent attacks. The latest data, presented in Dusseldorf and in publications, indicate no effect on lowering the elevated ALA and PBG levels in any of the eight patients. All developed antibodies to the virus vector. Note that gene therapy is disease-specific for AIP and not for the other acute porphyrias.

There are also some potential safety concerns that we won't enumerate here. But in sum, so far gene therapy hasn't worked in patients with AIP or the other -- and probably the other porphyrias. Next slide.

Now, what is the ideal therapy? Well, the ideal next-generation therapy should have an excellent safety profile; convenient administration, ideally subcutaneous and the potential for home use; a faster, longer-lasting effect for acute attacks to minimize the multi-day hospitalization; and it should be effective for prophylaxis in recurrent attack patients. Next slide.

In conclusion, acute porphyrias are a worldwide problem. They are pan-ethnic diseases. Attacks can be spontaneous or recurrent with life-threatening symptoms and a poor quality of life, with multiple long hospital stays and chronic and progressive neuropathic pain.

ALAS1-targeting in liver has been validated by liver transplantation in domino transplants and by heme’s mechanism of action -- in other words, the negative feedback inhibition. Finally, there is an unmet need for new therapeutic options with a better safety profile and faster onset effective for prophylaxis.

With that, I would like to introduce Desiree Lyon Howe, who is the Co-Founder and Executive Director of the American Porphyria Foundation. Dee?

Desiree Lyon Howe - American Porphyria Foundation - Co-Founder and Executive Director

Well, I want to share about the Foundation and its work. The Foundation began with two founders, me and a man named James Young, on my kitchen table. And today, we have 8,700 members, with over half of them as patients.

Our very first action was to locate the most esteemed experts in the country -- who, by the way, continued to serve as our scientific advisory board for the last 34 years. We have added some, of course, but I think it’s great that those who began with us remain. And that decision to rely on our board for all of our educational materials and programs has been key to the success, I believe, of the Porphyria Foundation.

From that board, we have recently created a Porphyria Research Consortium as part of the NIH Rare Disease Clinical Network. And these experts have been willing to assist us. It is very rare that we don’t consult with one of them on a daily basis. And as I noted, this commitment to ally ourselves with this prestigious group of specialists has been key to our tremendous success at the APF.

To assure that we continue to have the same caliber of clinicians, and scientists, and researchers, we created the Protect the Future program to train the next generation of experts. These young doctors are included in all of the efforts of the consortium. They share in the research, the publications, the physician and patient education programs, and even our APF media campaigns, which you will see later are quite extensive.
The APF and the consortium work closely on all of our research projects. We educate the patients about research, so that they are not as squeamish about joining in, and we locate them for the clinical trials and put them with the consortium. We teach them that they are medical heroes, and they are.

The other wonderful thing about this camaraderie that we have is that this collaboration has not gone unnoticed. We have received praise from NIH, FDA, Office of Rare Disease, and similar entities as a model for organizations to follow. Other organizations -- organizations like the Association of the American Medical Colleges -- have even asked us to write about our collaboration and about how we maintain good relationships, because it has been key. We've had an enormous success for a rare disease foundation.

The consortium also assists -- slide, by the way -- the consortium assists us by writing all of our patient education materials. They participate in our educational conference calls with physicians and patients. They attend our patient meetings. And having that -- having them author all of our materials has further validated our solid reputation among health care professionals and government departments. Slide.

Our experts also consult with patients around the world and their physicians. Recently, I was in China, and this very first slide I would -- my first day I was in a hospital. And the French doctor wanted to know all about porphyria. So I shared my case with her as she asked, as I will do with you now.

I was a teenager when I had my first attack. The abdominal pain was relentless. I was thought to be an emotional young woman with a tendency to hypochondria. And this pattern of monthly attacks, congruent with my menses, continued for the following decade. Doctor after doctor ordered basic tests to no avail. And my symptoms did not match my test results.

The pain was overwhelming and relentless, yet nothing showed on tests. I was given this hypochondriac tag, and once it was fixed on my records, it remained there from doctor to doctor. So I was basically ignored. And, by the way, I love doctors, so I don't mean that in any bad way. It was just -- how could they tell? There was nothing on the test.

So I was too embarrassed to go, and eventually I stopped seeing doctors until a family friend, a physician, told me that I was metallic gray and needed to stop that and come to his office. And I did -- but, unfortunately, every test once again came back negative, except that he could see I was having slight seizures. So he gave me what turned out to be an unsafe drug for porphyria, Dilantin, and that began a series of life-threatening events.

Foremost, the horrendous pain became beyond description. My best explanation is to tell people that it's like 1,000 flaming swords in my abdomen, burning and searing and scorching me. And I would scream, take me, God, please! And meant it. It was only when I was catheterized, and out poured this very telltale sort of purple/red/brown urine did my doctor have a clue that it was not blood, but porphyrin precursors. And he tested me for porphyria. When it was found positive, I was medic evaced at death's door to NIH. Next slide.

I was -- had very little hope for being able to live, but fortunately I was given hematin that stopped the attacks. Unfortunately, they continued; and I was hospitalized 100 times, paralyzed twice, 30 times in the intensive care, each memorable because of the horrific pain I described.

Unfortunately, hospitals would not keep hematin in their pharmacies. When I did have infusions, I would tend to get phlebitis, and there was still nothing to stop the attacks. So from misdiagnosis to treatment, my case was the plight of most patients. They are all very similar. So they are all very excited over this Alnylam treatment that would stop the attacks from occurring. Next slide.

Together, we are seeking to help change all of this, beginning with testing. You will see a young woman, desperate because all of her testing has been done incorrectly. And we are trying to help with that and with all of the treatment. So we began with great media efforts to find patients. All of the doctors help us in these media -- in these many media events, as you will see from this slide. Media campaigns are huge with the APF.

We also have a number of fundraising efforts, with fun being the edge. Slide. And awareness efforts. We include -- in national awareness week -- we include patients in this. And we let them use every means, whether it is getting out brochures to their own Facebook pages -- and interestingly, after that week is over, we have another onslaught of people who are diagnosed.
The experts help us -- next slide -- with all of our educational materials. They are excellent materials. They are award-winning materials. They also help us with our legislation efforts. Slide please.

In fact, the APF has [not] gone to Congress and the FDA. But as he said, as Dr. Desnick said, we are very instrumental in the first orphan drug act and the first orphan drug and have continued today to be involved in every research that has to do with rare diseases. And the last slide is that of a cross-section of a DNA.

So we try to show people and help them understand that even if they have a horrible disease, that we are here to support -- but also that they are very valuable to each other. They can help each other; they can help new patients; that they are just not a sick person isolated in the world. But they are what the Bible says is fearfully and wonderfully made, and they have so much to offer. That has been a tremendous help. If anything we have done, we have been a great support and taught them how to support one another.

Thank you very much.

Josh Brodsky - Alnylam Pharmaceuticals, Inc. - Senior Manager IR and Corporate Communications

Great. Thank you very much. We are now going to open it up for Q&A with Dr. Desnick and Desiree Lyon Howe. And as a reminder to those on the webcast, you can submit your questions by clicking the ask a question button located above the slide window on the webcast player. John, go ahead.

QUESTIONS AND ANSWERS

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Yes, let me just start, Dee, and begin by saying that your courage and your story inspires us to bring this medicine to patients in your community as fast as possible. And rest assured that we are going to do everything we can to do that. Thank you.

Desiree Lyon Howe - American Porphyria Foundation - Co-Founder and Executive Director

There is tremendous excitement. By the way, there was a slide that I did not have in here, and I am going to mention it because it was a slide of my husband Dick and my dog, sound asleep. And the reason I put that in there is because when they are asleep, the work of the APF continues -- because around the world, people come to the American Porphyria Foundation and the American experts for help. Not that there are not experts in other places, but around the world, they continue to come. So these patients are also excited about this new treatment. It is not just here in this country. It is everywhere.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Sure. That's great, Dee, to hear. Well, let me now turn to some of the questions that we have received during yours and Dr. Desnick's presentation. Quite a few are around diagnosis, actually; and let me try to synthesize some of the questions into a common theme.

I think one theme is the question of what are the key hurdles of diagnosis? How do -- I think probably this would be best initially by you, Bob -- key hurdles of diagnosis; how do you expect it to change; and then, will a new therapy emerging improve diagnosis? So maybe, Bob, you can start; and then Dee, if you want -- have any comments, you can add to that as well.
Thank you, John. Diagnosis is a major issue in the porphyrias. It is often considered a diagnosis of exclusion. The symptoms can be very vague. Often patients are misdiagnosed or underdiagnosed.

When they have the excruciating abdominal attack, and they show up in the emergency room, the first thing that is thought is appendicitis. And when -- doctors will even -- have even operated on patients in the past, even though the leukocytosis -- you know, they don't have a significant elevation of white cell count, which is typical in appendicitis.

What we have to do -- and the American Porphyria Foundation and those of us who are involved in porphyria research and clinical trials -- we have to educate and create greater awareness that this is a diagnosis you have to think of, particularly for the emergency room doctors; for the neurologists, who have these -- painful neuropathic pain and other symptoms. And when patients are symptomatic, it is very simple if they order the right test. Very often, they order porphyrins, and porphyrins aren't really the right test.

What they need to order is ALA and PBG. And if they order those two when patients are symptomatic, they will see a significant increase in the urine, and that will be diagnostic. There is very little that can -- there is really nothing else that's pathognomonic for acute porphyria. And that is key to the diagnosis.

Of course, if they are in between attacks, they can do DNA analysis; and we can look at the four different acute porphyria genes and identify specific mutations. So that is very effective as well and, also, that will pick up family members. That is another important point, is that these are dominant diseases and not every patient has either had porphyrinogenic drugs, or has fasted or dieted, or maybe had some other hormonal change that triggers the attack.

So it's very important to identify the other members of the family who have not had an acute attack, because they are susceptible. And they should be appropriately counseled and be aware that they have the disease and be careful about the drugs, make sure they are all safe when a doctor prescribes it, and also either wear an identification tag or be very much knowledgeable that they have this disorder and at risk for an acute attack.

I think the key is awareness and doctor education. And that's one of the things that the American Porphyria Foundation does by going to the different meetings, like hematology, liver disease, genetic meetings, emergency medicine meetings, etc. We just have to make doctors aware that these are diagnoses for which there is a current treatment and which there are other options emerging.

Great. Dee, anything to add to that perspective?

I'd like to just say that, interestingly, we had a doctor's wife who had this same problem of diagnosis. And she had removed her appendix, her gallbladder, her spleen, a complete hysterectomy and colon surgery. The only reason -- they put on her record that she was drug-seeking, and the only reason they took it off was because she was this physician's wife, and he assured them that she was going through this terrible pain. And that is how she had every one of these organs removed.

And the reason she was diagnosed was because she saw one of the media events that the APF -- I believe it was Mystery Diagnosis. And she went immediately to her husband, her physician, and sure enough, that is what her problem was.
John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Wow, okay.

Robert Desnick - Icahn School of Medicine at Mount Sinai - Dean, Genetics and Genomic Medicine and Professor and Chair Emeritus, Department of Genetics and Genomic Sciences

Being a geneticist, I can tell you that there are many patients that are undiagnosed. And until there's an awareness of the physician, the right -- and performing the right tests on the urine, the diagnosis often goes undetected. So we need to increase the awareness.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

So that's a good segue to another question that we received also related to diagnosis. Are there neonatal screening programs in the US or anywhere in the world?

Robert Desnick - Icahn School of Medicine at Mount Sinai - Dean, Genetics and Genomic Medicine and Professor and Chair Emeritus, Department of Genetics and Genomic Sciences

Not that I'm aware of. I think that in the future, there will be more genomic testing and that will lead to identification of the carriers of these genes, and then we will have a much more accurate diagnosis.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Dee, has your foundation had discussions around neonatal screening? Well, maybe she had to step out. Yes, that's not a problem. Okay, well, let's go to another question that we also received. And Bob, this would be good for you. Do you think there's a role for treating carriers of the disease? Or do you think it would be only used or this type of drug would only be used for patients that have an existing history of attacks?

Robert Desnick - Icahn School of Medicine at Mount Sinai - Dean, Genetics and Genomic Medicine and Professor and Chair Emeritus, Department of Genetics and Genomic Sciences

So I think that we don't fully understand the scope of the disease. And many of us believe that people who have the gene, who are heterozygous for these dominant diseases, but aren't symptomatic, may have other symptoms that just -- that are vague, like the neuropathic pain and the progressive neuropathy.

Up till now, that has not been studied. And one of the things that our Porphyrias Consortium, which brought together the six experts in the US and now we have added another three satellite sites of people that we've trained in our Protect the Future program, we are beginning to reach out and identify the members of the family who also have the gene and to determine -- to see them and to evaluate what medical issues they have. I wouldn't be surprised if we learned that there are patients out there who are high secreters of ALA and PBG who have never had an acute attack that brought them to diagnosis or brought them to the hospital who have other symptoms, like the neuropathic pain ones, that may be in line for treatment.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Interesting. So another question here, Bob, which I think you can help answer is, are there any known determinants for the severity of the disease? And I guess the question would apply, at least if I'm interpreting the question appropriately, to genetic, but also behavioral or acquired determinants. Can you comment on that?
Robert Desnick - Icahn School of Medicine at Mount Sinai - Dean, Genetics and Genomic Medicine and Professor and Chair Emeritus, Department of Genetics and Genomic Sciences

In the behavioral area, many patients will comment that stress will be an inducer of attacks. And in fact, the EXPLORER, the natural history study that's being conducted by Alnylam, has uncovered some sort of pre-symptomatic issues that we didn't really appreciate.

The more subtle aspects of the disease, the various components that will bring on an acute attack, we're learning a lot about that from the natural history studies and as well from the work of the Porphyrias Consortium. I think we're going to find that there are both physiologic and behavioral precipitants, as well as other genes, that might lead to those who have recurrent attacks. And in fact, that's one of the areas that we are aggressively studying in the Porphyrias Consortium. We want to understand what are the factors that lead certain patients to have acute attacks and others who have the gene not to have these dramatic and life-threatening attacks.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

That's helpful. Now one maybe last question before we turn it over to Bill for results related to our program is regarding gene therapy. You commented on gene therapy in your talk. Do you understand or is it understood what the level of ALS-1 transduction would need to be for gene therapy to be effective in acute intermittent porphyria -- I'm sorry, not ALS-1, but PPGD. What level would need to be achieved to have a therapeutic effect in the disease?

Robert Desnick - Icahn School of Medicine at Mount Sinai - Dean, Genetics and Genomic Medicine and Professor and Chair Emeritus, Department of Genetics and Genomic Sciences

Right. So two groups have studied the AIP animal model. And we have been able to show that getting in a significant overexpression of the corrective gene for AIP does eliminate the ability to induce attacks in the mouse model.

However, in the mouse you can get a lot of the AAV in. You can get probably 10% or more uptake. But you are getting overexpression that's very good. In the humans, they have gone up to 10 to the 13th particles with overexpressing enzyme and they haven't been able to affect the ALA or PBG. And I think that's very concerning. So up till now, they haven't had an effector that gets to enough cells to change it.

There's one other study that has been done by the Swedes, where they attempted to introduce isolated normal hepatocytes into the animal model. And in that case, they were able to reduce the ALA and PBG about 50% and they thought that they had at least 5% of the normal cells in the liver. They estimated that it would take more than 10% of liver cells transformed or the corrective cells in the liver, part of the liver mass, to actually really bring down the ALA and PBG to normal levels. But that's conjecture; there's no real data on that. And the mouse studies are the only ones who indicate that probably you need 30% or more.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Yes. I would think that's the case, given that heterozygous disease is pathologic and therefore it argues that you would need almost correct -- correction to near-normal levels, at the very least.

Thank you, Bob and Dee. And if you can stay on, we might have more questions for you at the end.

I'd like to now transfer it over to Bill Querbes, who is our project leader for this program, also the inventor of the drug as well. So it's a great pleasure to have him here and share our program progress. So, Bill?
PRESENTATION

Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

Great. Thanks, John. And thanks to both Dr. Desnick and Desiree, who gave a really nice introduction and overview of the disease.

I think it’s pretty clear from what they told you that there’s an enormous unmet need for prophylactic therapy in these patients that are experiencing multiple recurring attacks. At the current time, these patients can be very difficult to manage. They spend considerable time in the hospital, need regular heme and pain medications, and really have a very poor quality of life. And we think that our approach with a safe, subcutaneously administered EST GalNAc conjugate to block production of these toxic heme intermediates can make a really significant improvement in patients’ lives.

So just last week, we announced our initial interim Phase 1 data from this program and also presented some preliminary data from our natural history study that we are calling EXPLORE. And so, we are going to review that data here today.

So Dr. Desnick provided some introduction to disease pathophysiology. But just to speak a little bit more in detail about that, patients with the acute hepatic porphyrias had elevated levels of ALAS1, which cause increased blocks through the heme (inaudible) pathway, causing buildup of these toxic heme intermediates, ALA and PBG, that occur upstream of the mutated enzyme. In the case of AIP, this would be PBG-D.

And our therapeutic hypothesis for this program is to lower ALAS1 with ALN-AS1, to reduce the ALA and PBG production and thereby prevent the development of attack symptoms.

The data on slide 47 shows some preclinical data with ALN-AS1 in a phenobarbital-induced rodent model of AIP. So in this model, ALN-AS1 was given subcutaneously weekly for four weeks. The PBGD enzyme that’s mutated in AIP was lower in the liver using sRNA, and the animals were challenged with phenobarbital, a P450-inducing drug daily for four days, which mimics a drug-induced attack of porphyria. We then monitored changes in liver ALAS1 mRNA levels, as well as ALA and PBG levels in urine.

On the left-hand graph, what you can see is that phenobarbital treatment induces liver ALAS1 levels. However, pretreatment with ALN-AS1 dose dependently prevented these increases in ALAS1 mRNA levels. On the right-hand side of the slide, ALN-AS1 also dose dependently prevented the phenobarbital-mediated induction of these toxic intermediates, ALA and PBG.

So this is just a highlight or an example of our robust preclinical data that suggests that if we can lower ALAS1 in liver, we should have a dramatic impact on ALA and PBG production.

The next slide, slide 48, shows an overview of our Phase 1 study, which is currently ongoing. This study is a single ascending dose, SAD, and multiple ascending dose, MAD, single-blind, placebo-controlled study in patients who are asymptomatic high excreters of ALA and PBG. It’s important to remind people that healthy volunteers do not have significant levels of these heme intermediates, ALA and PBG. So this asymptomatic high excreter population provides a more stable population to assess safety in ALA and PBG lowering.

The dosing has been completed in the four single ascending dose cohorts, which is the data that we will be presenting today. The first MAD cohort is ongoing with two monthly doses planned, and we will explore a second MAD cohort and also have the ability to examine different doses or regimens and several optional cohorts in part A or B, as needed. After we have established good safety and identified an effective dosing regimen in parts A and B, we will move to part C, which is going to be a multiple-dose phase for 12 weeks in AIP patients that are having multiple recurring attacks.

So turning on slide 49 to give an overview of the safety that has been seen to date, ALAS1 has been generally well tolerated so far. There has been no serious adverse events, or SAEs, related to study drug or discontinuations. Other AEs reported were all mild to moderate in severity, with no dose-related trends and no events occurring in more than one treated subject. There was one mild, transient injection-site reaction or erythema that resolved within a couple hours.
There were no clinically significant lab abnormalities related to study drug. One patient did report an increase in liver enzymes CPK and myoglobin, which was attributed to an intensive weightlifting program. And after the patient stopped that weightlifting regimen, all of that subsided.

So turning to slide S1, one unique challenge of this program compared to maybe some other ones in our pipeline that many of you are familiar with is that our target, ALAS1, is not a secreted serum protein. Therefore, we cannot simply monitor PD with a protein [that aligns that] asset using serum drugs. So we took advantage of emerging data in the diagnostic and biomarker fields that liver cells secrete very high levels of membrane-bound vesicles or exosomes into circulation that contain mRNA, or micro RNAs, from the cells or tissues of origin, in this case hepatocytes. And this allows us to monitor ALAS1 mRNA changes in circulation without the need for a liver biopsy.

And the right-hand side shows a proof-of-concept experiment where following dosing with an ALS GalNAC conjugate in a nonhuman primate, we took liver biopsies or serum and compared the levels of ALAS1 mRNA. What you can see is a very tight correlation with the levels of ALAS1 mRNA knockdown in the biopsy as compared to the levels in serum and a really, really tight relationship there, suggesting that the serum levels of ALAS1 mRNA is very accurately representing what the levels are in the liver.

So this is a very exciting assay. It allows us to noninvasively measure direct ALAS1 target mRNA suppression. Now we can do this assay both in serum, as well as in urine. This has been used extensively in our preclinical studies to monitor kinetics of ALAS1 lowering, as well as recovery. And this is now being -- this assay is now being deployed both in our Phase 1 study and in our EXPLORE natural history study, which I will talk about more in a minute.

So turning on slide S1 to the data here, this is showing ALAS1 mRNA data monitored with the cERD assay I just mentioned, in this case in serum. And the first thing that we can highlight, at baseline we could detect a threefold increase in the ALAS1 mRNA levels in these asymptomatic high excreter patients on study as compared to those seen with some control, healthy volunteer patients. So this is another nice confirmation of our therapeutic hypothesis that ALAS1 increases lead to the overproduction of these toxic intermediates, ALA and PBG, which are elevated in these patients.

On the right-hand side, you can see that there’s nice dose-dependent lowering of the ALAS1 mRNA following a single dose of ALN-AS1. We see a mean maximum lowering of up to 44%, with a maximum of 59% seen in the 0.35 milligram per kilogram group. And the cERD data for the 1 milligram per kilogram cohort is not available yet at this time. And similar results to what we see here in serum have also been seen with urine, which further supports that this is adequately representing what is happening in the liver.

On slide S2, we show how the lowering of these ALAS1 mRNA has translated into impact on these heme intermediates, ALA and PBG. We see a very robust dose-dependent lowering of ALA and PBG following a single dose of ALN-AS1. This includes up to a mean maximum reduction of 77% and 73% lowering of ALA and PBG, respectively. In the 1 milligram per kilogram group that is still ongoing, we have seen up to 82% lowering of ALA and 93% lowering of PBG.

Additionally, the effect is quite durable, with the robust lowering of these intermediates lasting out to the latest time point we currently have, which is day 42.

And so, this is a pretty robust effect on these ALA and PBG intermediates. And I think the duration data that we’ve seen so far suggests the potential for monthly or even potentially quarterly dosing for prophylaxis in these patients.

On slide S3, just looking at an overlay of the relationship between the ALAS1 mRNA and the ALA and PBG, you can see a very nice, tight relationship between reduction of ALAS1 mRNA correlating with the dose-dependent decreases in ALA and PBG. And as you would expect, higher levels of ALAS1 mRNA reduction, you see greater decreases in ALA and PBG. And this was actually very beautifully predicted from our preclinical studies as well of that tight relationship.

So just to summarize what I’ve just told you on the Phase 1 study and talk briefly about next steps for the program, ALAS1 was generally well tolerated in this study to date. We’ve developed a novel method to monitor ALAS1 mRNA noninvasively that’s demonstrated upregulation of ALAS1.
upregulation of this ALAS1 that drives the overproduction of these intermediates.

fourfold over healthy volunteers, which again supports this hypothesis that in these patients that are having active disease, that there’s significant

found that using a certain method for looking at the ALAS1 mRNA that at baseline patients with recurrent attacks have an average increase of

PBG, or the ALAS1 mRNA that occur from a pace and space line visit during their attack or following treatment. On the upper part of the slide, we

On slide 58, we have been collecting a lot of important biomarker data for this program, looking at whether we can detect changes in either ALA,

attack situations.

try to mask some of the pain they experienced at 30%, as well as some use carbohydrate loading at 11%, which can sometimes help them in minor

outpatient office visits and infusion clinics to get heme. And the most common treatments of the attack were heme in 43%, using pain meds to

What was also actually surprising is that even patients that are using heme on a regular prophylactic basis -- often weekly, every other week, or

monthly -- still had an annualized attack rate of three, suggesting that these approaches are not fully protective at preventing attacks.

or back pain, the GI symptoms, tachycardia, or neuropathy. And at the time of this data cut, 101 attacks’ worth of data had been captured during

In the overall study design, there are two office visits, at the start of the study and at six months, that involve multiple questionnaires, and then

there’s follow-up phone calls that occur at two months and four months where they also mail in urine samples to monitor biomarker levels. And

we also collect additional information in terms of urine samples, as well as questionnaires during any attacks that these patients experience on the

study. And we think this data that we are going to learn about in this natural history study is going to be really important to the later-stage
development of this program.

So slide 56 shows some data that patients have reported with their screening questionnaires at their first visit. And we asked them the question of

what are the common symptoms that you experience during attacks. Some of these symptoms they reported were consistent with the literature,
such as severe abdominal pain, back or limb pain, GI symptoms, as well as some autonomic symptoms, such as tachycardia, sweating, et cetera.

What we did see is higher previously that reported level of anxiety and sleep difficulties, as well as some other things, such as these changes in red

urine color.

And I think Desiree mentioned this earlier, but perhaps one of the biggest surprises we asked is whether these patients experienced any symptoms in between their acute attack events. And almost 50% of the patients reported that they had persistent chronic symptoms that can include pain, GI problems, anxiety, highlighting that previously this had been considered a disease that only occurs during these acute flareups. But in reality, many of these people have many chronic symptoms and they don’t go back to being totally well in between the severe attack crises that occur.

On slide 57, we have been capturing attacks that these patients experienced while in the study that were defined as instances of severe abdominal or back pain, the GI symptoms, tachycardia, or neuropathy. And at the time of this data cut, 101 attacks’ worth of data had been captured during this EXPLORER study. Keep in mind that patients have been on this study for different periods of time, but up to 60% have reported at least one attack that we have been able to capture data on. Patients not using heme prophylactically had had an annualized attack rate of about four.

What was also actually surprising is that even patients that are using heme on a regular prophylactic basis -- often weekly, every other week, or monthly -- still had an annualized attack rate of three, suggesting that these approaches are not fully protective at preventing attacks.

These patients sought treatment in multiple locations, such as the ER inpatient ward. Some of them treat their symptoms at home, as well as outpatient office visits and infusion clinics to get heme. And the most common treatments of the attack were heme in 43%, using pain meds to try to mask some of the pain they experienced at 30%, as well as some use carbohydrate loading at 11%, which can sometimes help them in minor attack situations.

On slide 58, we have been collecting a lot of important biomarker data for this program, looking at whether we can detect changes in either ALA, PBG, or the ALAS1 mRNA that occur from a pace and space line visit during their attack or following treatment. On the upper part of the slide, we found that using a certain method for looking at the ALAS1 mRNA that at baseline patients with recurrent attacks have an average increase of fourfold over healthy volunteers, which again supports this hypothesis that in these patients that are having active disease, that there’s significant upregulation of this ALAS1 that drives the overproduction of these intermediates.
Using the cERD method in serum, we could detect a statistically significant increase in the liver ALAS1 mRNA levels during the attack phase from their baseline, and then we can see a decrease in ALAS1 mRNA levels that go down following treatment, in many cases, with heme.

In a smaller subset of patients on the bottom, where we had complete sample sets -- so we had sample sets at their baseline, during their attack, before they got heme, and then post-treatment with heme, we could detect increases of ALA and PBG at these attack peaks and decreases below baseline after they get heme treatment. So clearly in emerging data sets here, we're continuing to monitor attacks throughout the rest of this study, but highlight really the importance and potential of these assays to serve as attack biomarkers moving forward.

So just skipping to summaries here, we showed you some exciting Phase 1 results, that we can actually lower our ALAS1 target and show decreases in these toxic heme intermediates, ALA and PBG, that drive attacks. We're also learning very important things in this natural history study that will really help in the design and execution of the later development for this program.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Great. Well, thanks, Bill. We had a couple questions come in that I think we will start with these that are perhaps most appropriate for both Dee and Bob. Dee, are you back on the line? Were you able to come back on? Okay, it doesn't sound like that.

So, Bob, we're going to go to the question for you, which is if heme works by lowering ALAS1, why doesn't it work sometimes? And does that argue that ALAS1 lowering may not always be the right answer or the answer?

Robert Desnick - Icahn School of Medicine at Mount Sinai - Dean, Genetics and Genomic Medicine and Professor and Chair Emeritus, Department of Genetics and Genomic Sciences

Well, that is the mechanism that we think it works on by adding to the free heme pool in the liver. But some patients may need more and maybe that's why it doesn't work as well. So that is a problem that we have, particularly for recurrent patients.

Desiree Lyon Howe - American Porphyria Foundation - Co-Founder and Executive Director

It may also be when the heme is given.

Robert Desnick - Icahn School of Medicine at Mount Sinai - Dean, Genetics and Genomic Medicine and Professor and Chair Emeritus, Department of Genetics and Genomic Sciences

That's true.

Desiree Lyon Howe - American Porphyria Foundation - Co-Founder and Executive Director

Sometimes a doctor does not want to give it until everything else has been done.

Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

(multiple speakers). There's also some data from the French group that suggests that chronic heme infusions can lead to induction of heme oxygenase. And so, that can further tip the balance into a more attack-prone state because they are continuing to manage the influx of heme with the heme oxygenase upregulation.
**John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO**

That's interesting, good. And Dee, so nice to hear your voice back. We actually had an interesting question that I wanted to ask you is whether or not the ATF has engaged with the FDA on discussing clinical endpoints and trial designs and approaches for new medicines in porphyria. No?

Maybe, Bob, do you know the answer to that question?

**Robert Desnick - Icahn School of Medicine at Mount Sinai - Dean, Genetics and Genomic Medicine and Professor and Chair Emeritus, Department of Genetics and Genomic Sciences**

So we have been to the FDA, but not about the acute porphyrias. We have been talking to them about other porphyrias, and I think that we've had very effective sessions with the FDA over these other porphyrias by bringing patients who share their experiences. And I think that's something that we have to do with the acutes as we move forward.

**Desiree Lyon Howe - American Porphyria Foundation - Co-Founder and Executive Director**

I'm so sorry, but when I heard you, it was sort of intermittent. I didn't get the whole entire question. But we have actually talked frequently over the past years about acute porphyria and acute porphyria treatments, including Panhematin and heme [marginate], et cetera, (multiple speakers) and the need -- and also a need for other treatments. So it's on their radar screen, for sure.

**John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO**

Good, terrific.

**Robert Desnick - Icahn School of Medicine at Mount Sinai - Dean, Genetics and Genomic Medicine and Professor and Chair Emeritus, Department of Genetics and Genomic Sciences**

Dee, I mentioned that we have had some very effective sessions with the acute porphyrias -- sorry, with the cutaneous porphyrias where we had patients who educated the people at the FDA about their chronic problems.

**John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO**

That's very helpful. Then the other questions I've got, I think, probably would be best directed to Bill. So there are some questions here that relate to the program status. One quick question is, will we present more data for the program? And what are the plans there, Bill? Do you want to answer that?

**Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research**

Yes, sure. I think we have guided that sometime next year, we will probably present them next time, once we actually have full data sets from part A and part B, and then, eventually, once we have data from part C. So sometime in 2016, I think, is --

**John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO**

Yes, that's great. Okay. And then, a couple questions here. Will you do a Phase 2 study or go direct to a Phase 3? And if you go direct to a Phase 3, what does that program look like? How many patients, what type of endpoints? What is the current thinking there?
Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

Sure. So I think given the unmet need here and the size of this patient population, I think we would move directly from this initial Phase 1 study into a pivotal study.

I think part of what we are learning from this EXPLORE study is how to define endpoints that we would need in a pivotal. And I think we've talked about looking at number of attacks or frequency of attacks. Other things we would look at are hospitalizations, heme use, pain med use, additional things we would look at.

And I think it's really going to all come down to is how exactly we are going to define -- the definition of an attack as an endpoint, so whether that will actually entail a set of symptoms, whether it will entail a set of symptoms, as well as some biochemical or biomarker changes as well that are predictive of an attack. And really, I think our EXPLORER study is going to really help inform that in greater detail.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Great. And a somewhat related question is, will patients in EXPLORER be eligible to be enrolled in either part C of the Phase 1 study or into your pivots?

Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

Absolutely. And I think we're learning a lot about these patients in EXPLORER. And it is our assumption that after they finish EXPLORER, they would certainly be able to participate in those other studies.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Great. That's good. Okay. So some more questions here, Bill. The level of mRNA silencing that has been achieved is around 50% or so to date. Do you expect to see more silencing of the ALAS1 mRNA?

Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

Sure. I think a couple of things about level of ALAS1 suppression. So the first thing to keep in mind I think that's a really important point is that, as we showed here both in the Phase 1 patients, as well as in the EXPLORER patients, is that they all have upregulation of ALAS1.

So our goal here is not to slam ALAS1 from normal levels to the floor; it's to bring these elevated patients back down into the normal range (inaudible) ALA and PBG. And I think that's really what we're seeing.

So taking someone that's two or threefold upregulation, bringing them down even 50% we can see is a very dramatic impact on ALA and PBG. So I think more moderate changes in ALAS1 will lead to very dramatic changes in ALA and PBG.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Yes, that seems pretty clear. So basically, it's just taking the induced levels and normalizing those --

Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

Correct.
John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

-- essentially is what is needed. But do you think you will get further decreases in the 1 milligram per kilogram group?

Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

Yes. So preclinically, we have actually looked at this in quite great detail. And what’s interesting about this pathway is we can lower the target to about 20% levels or 80% suppression in a naive animal.

And what’s interesting is that even when we go to very, very doses, we never get lower than that 20% floor. So we think that there’s some endogenous safety mechanism of pathway feedback that would prevent us from going to any dangerously low level of ALAS1, which could have an impact on heme production and hemoprotein function.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

And another related question is, what is the on-target risk? In other words, what happens if you go too far with ALAS1 silencing? Is there a potential risk of that?

Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

Sure. So, obviously, it’s a common question that we get from a lot of experts in the field -- would you decrease ALAS1 too low and then impact hemoprotein function? What will that do to the heme-dependent enzymes in the liver, such as P450s that are responsible for drug metabolism and other enzymes?

And I think from our preclinical studies, all the way from rat up to monkey, we did a lot of studies looking at high levels of ALAS1 knockdown, what happens to the levels of activity of heme-dependent enzymes. And we really haven’t seen any decrease in enzyme activity or decrease in actual levels of those enzymes or change in the levels of those enzymes. So I think we feel, knock on wood, relatively good about as much as we could do preclinically to try to derisk that.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

That’s great. Is there any way to monitor that in patients? P450 activity, changes in P450 activity?

Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

I personally feel that monitoring the ALAS1 levels is going to be the most sensitive, right, in terms of knowing where they start and how far they can be lowered. As long as you are not -- you are staying above that 15%, 20% level of suppression, I think we would feel pretty good about the safety there.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Great. Now there was one patient in the study that had a serious adverse event reported, abdominal pain. Was that a porphyria attack?
Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

So maybe I can just provide a little more general color on that one patient. So this was a patient in the 0.1 milligram per kilogram cohort. This event occurred about 29 to 30 days post dose. So this was on day 29, just the actual history. The patient was at a wedding and was extremely hungry. He was too busy to eat during the day. They ate three meals.

He went to the emergency room early the morning after, on Saturday morning. Because this patient had had an attack eight months prior, they got glucose and pain meds because of the porphyria history and to play it safe. Symptoms resolved very quickly. They were held overnight for observation and discharged the next day.

At the time of the event, luckily that was -- fortunately, in this case, this was a day after their day 28 visit. At that time, the ALA and PBG levels were down between 75% and 80% and there was about a 35% decrease in ALAS-1 at that time.

And at the DSRC meeting, the PI deemed the incident unlikely related to study drug. And she didn't believe it was related to porphyria for a few reasons, one being that typically these symptoms come on very gradually, they last much longer, and people usually can't eat when they have a porphyria attack. They have very bad nausea, vomiting. So there was just several reasons why this didn't seem to be a porphyria event.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

All right, that's helpful. Let's see now. One question is, does the ALAS1 -- or does the ALA and PBG lowering that we see in the study, does it normalize, ALA and PBG, in some of those patients? These are highly excreter patients that we -- actually achieve normalization of ALA and PBG.

Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

We actually did. At the higher dose cohorts of 0.35 and 1, we are getting these patients -- they actually start at quite a range of 3X above normal healthy levels, up to 12 to fifteenfold. And so, we have brought many of those patients back down to within very close, either twofold or less, which is really our target level.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Another question here is, how many patients will you enroll into EXPLORER?

Bill Querbes - Alnylam Pharmaceuticals, Inc. - Associate Director Research

So our target number of patients is 100. So we are feeling pretty good in the next several months of hitting that number.

We've given patients the opportunity to go from six months on study and then to stay for an additional six months to collect additional data, if they so desire. And we do have the potential to let it go over 100 if we think that we are obtaining valuable data and we want to continue to monitor a larger number of patients.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

And a related question that has been asked is, how many sites have --
Sure. This is a large number of sites. I think we are up to something like 18 to 20 sites, so we have six sites in the United States, as well as I think now about 12 sites through a lot of different European countries.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Good, good. Well, there aren’t any other questions. So I think what we should do at this point is certainly thank Dr. Desnick and Desiree for joining us. I think we start there and thank them very much. And, of course, thank all of you. I’m going to turn it over to Josh now to make some final comments. Josh?

Josh Brodsky - Alnylam Pharmaceuticals, Inc. - Senior Manager IR and Corporate Communications

All right. Thanks, John. This concludes our RNAi Roundtable for today. The replay and slides will be posted on the Capella section of the Alnylam website later today, with the transcript to follow shortly thereafter. And all of the RNAi Roundtables that we hosted over the past couple of months will be archived and available on Capella for your future reference.

So thanks, everyone, for joining us and have a great day.

John Maraganore - Alnylam Pharmaceuticals, Inc. - CEO

Thanks, everybody. Bye.