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Alnylam Pharmaceuticals, Inc. (ALNY)

Investor Meeting - Givosiran, in Development for the Treatment of Acute Hepatic Porphyria

CORPORATE PARTICIPANTS

Christine Regan Lindenboom
Vice President-Investor Relations & Corporate Communications, Alnylam Pharmaceuticals, Inc.

Akin Akinc
Vice President & General Manager-Fitusiran, Alnylam Pharmaceuticals, Inc.

Srikanth Nagalla
Program Director, Hematology Oncology Fellowship Program, Harold C. Simmons Comprehensive Cancer Center

Jae B. Kim
Vice President-Clinical Development, Alnylam Pharmaceuticals, Inc.

MANAGEMENT DISCUSSION SECTION

Operator: Good day, and welcome to the Alnylam Pharmaceutical's RNAi Roundtable. Today's conference is being recorded. At this time, I would like to turn the conference over to Mrs. Christine Lindenboom. Please go ahead.

Christine Regan Lindenboom

Vice President-Investor Relations & Corporate Communications, Alnylam Pharmaceuticals, Inc.

Good morning, everyone. Thank you for joining us for today's RNAi roundtable where we'll be discussing givosiran in development for the treatment of acute hepatic porphyria. I'm Christine Lindenboom, Vice President of Investor Relations and Corporate Communications at Alnylam.

With me today are Akin Akinc, General Manager of the Givosiran Program; Dr. Jae Kim, Vice President of Clinical Development; and Dr. Sri Nagalla, Associate Professor of Internal Medicine, Medical Director at the Blood Disorders Clinic and Program Director of the Hematology Oncology Fellowship at UT Southwestern Medical Center.

Today's RNAi roundtable is the second in a series of round tables that we are hosting this year. Today's event is expected to run about one hour. Akin will moderate a Q&A session at the conclusion of the presentation. If you'd like to submit a question, you could do so at any time during the event by typing your question in the Ask A Question field.

Finally, as a reminder, we will be making forward-looking statements and we encourage you to read our most recent SEC filings to have a more complete discussion of our risk factors. And with that, I'll now turn it over to Akin.

Akin Akinc

Vice President & General Manager-Fitusiran, Alnylam Pharmaceuticals, Inc.

Thank you, Christine. Alnylam has been working for the last 17 years to develop RNAi therapeutics as an entirely new class of innovative medicines based on Nobel Prize-winning science, with the technology that offers the ability to silence any gene in the genome with a potent and durable mechanism of action. Using this technology, we've been able to build a product engine for a sustainable pipeline and now, RNAi therapeutics are commercial, with the approval and launch of our first medicine last year. This slide shows the Alnylam clinical development pipeline, which is focused in four strategic therapeutic areas: genetic medicines, cardiometabolic diseases,

hepatic infectious diseases and now, through the initiation of preclinical programs, the CNS and ocular disease space. Our first product is ONPATTRO, which was approved last year for the treatment of hereditary ATTR amyloidosis. And today, we're going to be speaking about givosiran, which is in development for acute hepatic porphyria and earlier this year, we had a positive readout from our Phase 3 trial, ENVISION, which Jay will cover later on in the roundtable. And this program is now in registration.

And I'll just briefly talk about – just remind everyone of the therapeutic hypothesis behind givosiran as Dr. Nagalla will describe shortly. ALAS1 protein induction in liver in the context of Acute Hepatic Porphyria gives rise to an elevation of neurotoxic metabolites namely, ALA and PBG that are causal for porphyria symptoms. Givosiran is a GalNAc-conjugated siRNA that targets ALAS1 in the liver, reducing the levels, thereby lowering ALA and PBG as a means to prevent attacks and ameliorate disease symptoms.

And with that brief introduction, I'll now turn it over to Dr. Nagalla.

Srikanth Nagalla

Program Director, Hematology Oncology Fellowship Program, Harold C. Simmons Comprehensive Cancer Center

Good morning everybody; so I'll give you an overview of acute hepatic porphyrias. So what are porphyrias? These are caused by – these are a set of diseases that are caused by enzymatic defects in the heme synthetic pathway. Now heme is part of hemoglobin. It's part of myoglobin. It's part of multiple enzymes in the body. So this is a very important [indiscernible] (00:04:00) and a defect in the synthesis of heme results in multiple diseases or disorders like porphyrias. Now the problem here is, it's very challenging to diagnose porphyrias, especially acute hepatic porphyrias, because the symptoms and signs are very nonspecific because the patient – if you look at the last bullet point on the slide, the patient can actually present to neurology because they have neuropathies, they can present to gastroenterology because they have acute abdominal pain, or finally they could be referred to hematology because people are not able to figure out what's going on. They go to primary care, they go to psychiatry because they have psychiatric symptoms and signs and lot of patients end up repeatedly in the emergency room.

So it's going to be challenging and it takes maybe months, maybe years sometimes for a patient to get a diagnosis. This could be classified – porphyrias could be classified as acute hepatic or erythropoietic. So in other words, I view it as acute or chronic porphyrias. We will be focusing only on the acute hepatic porphyrias in this section.

In the next slide, you could see the heme synthetic pathway. So there are a series of steps starting with glycine and succinyl CoA and the last step is the production of heme. So just before that, the iron gets incorporated so that you form heme and then it can join with globin to form hemoglobin or it could become myoglobin or it could become many of the enzymes that are needed in the body. And if you look at it, the ones that are highlighted, those are the enzymes in the box, they're highlighted – those are the four enzymes and the disorders that comprise the acute hepatic porphyrias. For example, we have the ALA dehydratase-deficiency porphyria due to defect in the delta aminolevulinic acid dehydratase. That is the porphobilinogen deaminase defect that can give rise to acute intermittent porphyria. There is coproporphyrinogen oxidase defect that gives rise to hereditary coproporphyria, protoporphyrinogen oxidase defect that gives rise to variegate porphyria. So – and then apart from that, the ones that are not highlighted are some of these chronic porphyrias. So you can see there is series of steps, but the most important thing I would like to point out is the first enzyme, which is the aminolevulinic acid synthase because that's kind of like the rate-limiting step. So lot of these defects or lot of these symptoms that I was just telling you, the signs that I was telling you earlier come due to the accumulation of some of these byproducts.

For example, like in the figure, you can see the second step is the delta aminolevulinic acid. After that, it's the porphobilinogen. So, these can get accumulated in the body and [ph] bales (00:07:11) could work as toxins to nerves and to other systems, leading to lot of these symptoms and signs. Now the ALA Synthase, if it's – if we're able to manipulate it, then we could decrease the production of these, especially when there are defects distilled to some of these byproducts.

So going to the next slide, as I said, there are four acute hepatic porphyrias, the acute intermittent, the hereditary coproporphyria, the variegate porphyria, the ALA dehydratase-deficiency porphyria. Out of these, the most common thing whenever people say, okay, what's the classical acute hepatic porphyria, they're talking about the acute intermittent porphyria because majority of the patients have it, but the others can also occur. Now heme synthesis, 85% of it happens in the bone marrow, the rest in the liver, okay. So, ALAS1 or ALA Synthase 1 is the rate-limiting enzyme for the heme synthesis in the liver and then you have a separate ISOPOM like ALAS2 for the bone marrow.

Now, heme, whenever you have enough heme, it represses the synthesis of the ALA Synthase 1 messenger RNA; so it decreases the ALA Synthase 1 and in that way, the messenger RNA also goes down. And conversely, many drugs that induce the hepatic ALA Synthase 1 also induce some of these CYP genes. So, for example, any of these CYP inducers could also cause increased ALA Synthase 1 induction and that could be a problem. For example, if patients are on certain drugs, they could have an exacerbation of their porphyria attack because the ALA Synthase 1 is routing lot of the glycine and succinyl CoA into the heme synthetic pathway. And then there are defects in some of the enzymes I showed you that are downstream. So, then you start accumulating all these toxins because it's not going all the way through to heme. And you have all these initial toxins that are accumulating. So, lot of drugs can induce attacks. And there are other things, exacerbating factors that can induce attacks, everything depending upon the key rate-limiting enzyme, which is ALA Synthase 1

One on the next slide, it's just, whatever I told you, it's just, I'm sorry, I think it's slightly blurry but it's predicting a little bit blurry but if you look at it, the heme which is in the center turns off the mitochondrial ALS synthase and also it is turning off or that it causes degradation of the ALA Synthase RNA. So, just putting all the things that I just told you in a picture form, this is how it looks like.

On the next slide, we're going to be talking about the various clinical manifestations of an acute porphyria attack. Now, you can see in the central nervous system, you could have hallucinations or you could have an anxiety attack. It could get as worse as patients having seizures. And then in the peripheral nervous system side, you can have pain related to peripheral neuropathy, you could get respiratory weakness. On the autonomic side, you could have abdominal pain. I mean patients present with recurrent abdominal pain, they have multiple CT scans or MRIs, nothing shows up and some patients unfortunately have had a cholecystectomy, which is removing the gallbladder. They have their appendix taken out. They have a spleen taken out. They have multiple exploratory laparotomies. But there is no cause for this pain.

And these are all some of the clues that physicians need to think of when this is happening, could this be an acute porphyria that we're dealing with? Patients could commonly present with high heart rate, tachycardia, or high blood pressure, hypertension. They could get constipation or they could just be vomiting. So, I mean if you look at it, these symptoms and signs are present in multiple disorders. It's not just – so it's tough for a physician, who is dealing with the patient with these symptoms to suddenly think of porphyria unless they're educated and they know about this disease and they're aware of this disease.

On the next slide, I want to show you that it's not only the short-term side effects; it's not this acute side effect just because we called it acute porphyria, it's not just acute symptoms and signs, but there are long-term consequences from acute porphyrias. You could have renal failure, ending up on dialysis. You could have high blood pressure leading to cardiovascular damage. You could have liver damage resulting in liver cancer and gallbladder cancer. You could have neurological damage, you could have depression or you could also be suicidal. So there are a lot of long-term effects from acute porphyrias. How do you diagnose acute porphyrias?

So first thing is you're looking for these neurovisceral complaints. As soon as you have a patient with neurovisceral complaints, the things that I told you the neuropathies, the abdominal pain, the hypertension, the tachycardia, you don't have any other explanations, please we tell the physicians to first think of acute hepatic porphyrias. And then, the first and simple test which is often done wrong is a urine PBG or porphobilinogen, but unfortunately in practice, lot of physicians send out urine porphyrins and that's where the diagnosis gets delayed. But if we can educate our physicians, then that urine PBG is a first test, then if it's elevated multiple times, multiple folds like usually the normal is 2 or 2 to 4, most patients would have 10, 50 or even 100s in terms of the PBG.

So if it's positive, you say it could be acute intermittent porphyria, hereditary coproporphyria or variegate porphyria. There's one acute porphyria you would miss with just getting the urine PBG. And if you still suspect that, we get what is called as urine ALA or aminolevulinic acid. And of course, the best is to do genetic testing for these disorders which, through various organizations, it's easy nowadays and even Alnylam, I've used Alnylam in the past for getting some of the genetic tests done. So I think if you think about it, there are multiple ways you could actually get to a diagnosis. On the next slide, there are biomarkers for disease activity, and as I was telling you, the common biomarkers are the ALA and PBG which is, just you do them in the urine, and they're elevated multiple fold and then you know that the patient is having an acute attack of porphyria. But again, there are a lot of difficulties in obtaining them because labs don't have it in house or the hospitals and clinics don't have it in house, so it has to be sent out. It has to be done properly. So there are some challenges there.

The next thing is measuring the ALAS1 mRNA, which is even more challenging because that's definitely not available commonly. But if you get these things and you treat the patient appropriately with something that can inhibit or can repress the ALA Synthase 1 like hemin or givosiran, then you could see the ALA, PBG the ALAS1 mRNA, everything going down actually and that tells you that these treatments are effective at least for an acute attack and sometimes for – as a prophylactic agent.

So treatment of acute attacks next slide, we discontinue the drug precipitating the attack. So if there are drugs that are inducing the CYP enzymes that's causing an attack, we discontinue it and we carbohydrate load them because when patients are fasting or they have – they are running low on carbohydrates, that actually induces the ALA Synthase 1, so loading with carbohydrates represses it. You could give intravenous hemin, which down-regulates the hepatic ALA Synthase 1 and then again, as I said, down-regulation of that is – that enzyme is the key to treatment of an acute attack.

On the next slide, what are the current approaches for the prevention or treatment of acute attacks? We eliminate trigger factors and there are multiple trigger factors, sometimes it could be the menstrual cycle, it could be drugs, as I say, it could be fasting, so whatever is causing that, we educate the patient on that. Gonadotropin-releasing hormones can be used for suppressing the menstrual cycle, so that the menstrual cycle-related attacks become less common. We could give hemin prophylaxis weekly or twice-weekly. It's – hemin is very short – it's short-acting. So it has to be done at least weekly for it to be effective, but in most instances, it has to be done twice-weekly. Again, it's an intravenous drug, sometimes access becomes – like venous access becomes a challenge. So we may have to put a port in the patient or we may need to put a center line in the patient; those get infected. So there are a set of challenges with doing hemin prophylaxis regularly, of course, because ALA Synthase 1 and

– or all these hepatic porphyrias, they're all happening in the liver, if you take out the patient's liver and give them a new liver, you could cure this, but it's got – it's a very morbid procedure, it's got a lot of mortality. So this is a last resort. Gene therapy was tried and the current gene therapy that was tried was not effective at this time, but I'm sure there are going to be other options in the future. We could do gene silencing, so the ENVISION Phase 3 study of givosiran is complete and regulatory reviews are underway.

On the next and the last slide, we can talk about what are the unmet needs in acute hepatic porphyrias. Though the current treatment options, so mainly what do we have right now? We try to remove the triggers and everything and we treat with hemin. Now hemin as I said, if it has to be done weekly or twice a week, it's an irritant and it can cause iron overloading and it can – it needs venous – a proper venous access, so which means you need to present a line, so there are a lot of challenges with that. But again, we use it. We use hemin regularly in lot of patients to keep them out of attack. So it's used, but again it's not the best, but that's what we have right now.

There are no currently approved prophylactic agents, meaning hemin is actually for acute attacks, but we use it even as a prophylaxis to prevent attacks. And it's a – the current treatment is long – short-acting, but some long-lasting therapies with long-lasting effects that can last for weeks would definitely be a great boon to the patients and it would make it very convenient for them. And we need – we have to do continued research in this area. This is especially very important for our patient population.

I think that might be my last slide, so I'll turn it over to Jae Kim.

Jae B. Kim

Vice President-Clinical Development, Alnylam Pharmaceuticals, Inc.

Thank you Dr. Nagalla. And as you mentioned, the next speaker will be Dr. Jae Kim. Jae?

Jae B. Kim

Vice President-Clinical Development, Alnylam Pharmaceuticals, Inc.

Thank you, Akin. Next slide please. The Phase 3 ENVISION study was designed to be the definitive study on efficacy and safety of givosiran in acute hepatic porphyria. [indiscernible] (00:19:11) a landmark study and the most rigorously designed and executed study in this disease space. It had a truly global footprint with 94 patients enrolled at 36 sites in 18 countries. It was a randomized, double-blind, placebo-controlled study in patients diagnosed with AHP and these patients who enrolled were randomized one-to-one to six-months double-blind treatment of givosiran administered monthly in subcutaneous injections or placebo.

The endpoints were rationally designed and informed by a patient-centric approach, the primary endpoint reflected the greatest burden of disease, which was composite annualized attacks requiring hospitalization, urgent healthcare visits or hemin administration at-home in patients of AIP at six months.

The secondary endpoints included aminolevulinic acid and porphobilinogen levels which are the cause of neurotoxic factors that drive the disease, hemin doses, and also tested here is a composite annualized attacks in all AHP subtypes, other symptoms that were evaluated in addition to the physical component summary of a symptom PRO called SF-12, all eligible patients were also rolled over into the open-label extension period.

Next slide, please. This slide summarizes the demographics and baseline characteristics of patients enrolled in ENVISION. And it shows that these characteristics and demographics were well-balanced between those patients randomized to placebo and givosiran. These were largely female patients which represents really the disease.

And also the study succeeded in recruiting some of the very, very rare subtypes including hereditary coproporphyria and variegate porphyria and we show a distribution of patients across North America, Europe and other countries.

Next slide, please. The baseline disease characteristics and comorbidities of AHP patients were summarized here, and it shows patients in ENVISION represented the type of patients seen in clinical practice and also reflect the burden of the disease that these patients suffer.

Patients had a median of three composite attack rates during the six months prior to screening. Approximately 40 patients of – approximately 40% of patients were on hemin prophylaxis prior to study and about half of these patients experienced chronic symptoms between attacks. Disease related comorbidities included liver disease, chronic kidney disease, neuropathy and iron overload.

Next slide. ENVISION met its primary efficacy endpoint of reduction in annualized attack rate in patients with AIP and met so with a high degree of significance with a p-value of 0.000000006, my favorite part of the presentation.

On the lower left hand panel, we see a mean 74% reduction in composite attacks and also in the lower bars, you see that there were consistent efficacy favoring givosiran across all components of the primary endpoint. Also in the middle panel, we show a 90% reduction in the median composite attack rate. And in the right hand panel, we see achievement of three fold increase in patients who achieved sleep remission from attacks that is approximately half of the patients on givosiran resulted in zero attacks or being completely attack-free.

Next slide please. This slide summarizes all of the pre-specified subgroup analysis of the primary endpoint, and also shows that there was a consistent effect across all subgroups. Notable was also the impact on the patient subgroups who were on prior human prophylaxis, who had historical attack rates that were high or low; and a consistent effect of inpatients who had between attacks chronic pain or chronic opioid use.

Next slide, please; givosiran also demonstrated statistically significant differences in multiple secondary endpoints with significant reductions in mean ALA at month three and month six, and PBG at month six, significant reduction in mean annualized days on hemin in AIP. And also a significant result in mean composite attack rates in all AHP. There were also nominally significant improvements in daily worst pain in AIP and the physical component summary of SF-12.

Next slide, please. As Dr. Nagalla had mentioned, ALA and PBG are the key cause of neurotoxic intermediates that are responsible for AHP disease manifestation. Givosiran showed rapid, robust and sustained reductions in urinary ALA and PBG over six months. And showed a robust magnitude of reduction in mean or median ALA and PBG as shown in the box here; red exemplifies the placebo arms and blue it shows the mark reduction achieved with givosiran treatment.

Next slide, here we summarize the adverse events in AHP patients and patients randomized placebo or givosiran. We see that the overall incidence of adverse events were similar between placebo and givosiran. There were four serious adverse events on placebo and 10 on givosiran, that the details of which we will discuss in the next slide. There were zero deaths in the ENVISION study. All 94 patients in ENVISION completed the six-month randomized double-blind period of the study. There was one patient who had discontinued from givosiran for an ALT elevation and met protocol stopping rules.

Next slide, here we summarize the serious adverse events in AHP patients and placebo and givosiran and are listed here. As you'll note there is no specific pattern that is particularly notable and most were single events. Of

note, there were two SAEs in givosiran patients reported as a study drug related. One abnormal liver function test as we've discussed and one chronic kidney disease, no SAEs in placebo patients were reported as study drug related.

There were two chronic kidney disease AEs that were considered serious due to elective hospitalization for diagnostic evaluation, [ph] i.e., (00:27:24) they received renal biopsies. These biopsies in both patients were consistent with the underlying disease. There were no signs of immune complex or primary glomerular renal disorders.

Here we show the common adverse events that occur in greater or equal to 5% difference in treatment groups. In the upper portion of the table, we show those with higher frequency in the givosiran group and those with higher frequency in the placebo group are shown in the lower part of the table.

As we look at safety, there were two types of events that may [ph] require further (00:28:06) discussion which we will show in the next slide.

And here we summarize the impact of givosiran on liver transaminases and renal function. ALT greater than three times upper limit of normal occurred in seven givosiran patients and one placebo patient. As discussed before, one patient was discontinued due to meeting protocol-defined stopping criteria. One patient had a dose interrupted due to protocol-specified rules and resumed dosing with givosiran without recurrence of the transaminase elevation, and five patients who had transaminase elevations have resolution during ongoing givosiran treatment. There were no Hy's Law cases.

ALT elevations were mild to moderate and occurred approximately three months to five months after givosiran treatment began. And in most cases, the ALT elevations resolved or stabilized by month six.

Also notable were seven patients on givosiran and two on placebo had renal adverse events of increased creatinine or decreased eGFR, and five AEs of CKD in givosiran patients.

Most of these AEs were mild to moderate in severity and resolved without treatment introduction. Generally these were small increase in serum creatinine, median change was 0.07 milligrams per deciliter monthly and decreases in eGFR was givosiran that resolved or stabilized at month six.

Here we summarize the data from the open-label extension period of the Phase 3 ENVISION study. In blue, in both the left hand panel showing monthly attack rates and in right hand panel urinary ALA, we show a maintenance of reduction in composite porphyria attack rates and urinary ALA levels in those patients who continued on givosiran during the open-label extension.

As a confirmation of the initial randomized efficacy shown in the six month double-blind treatment period, there was a rapid and sustained lowering of composite porphyria attacks and ALA levels in those patients initially randomized to placebo who crossed over to givosiran in the OLE period as demonstrated of these red lines on the plots. The safety profile was consistent with the observed profile in a double-blind period.

Next slide please. And so we summarize the results of the ENVISION Phase 3 study and givosiran resulted in the 74% mean reduction in annualized composite attack rates in AIP patients, which showed consistent results in reduction of porphyria attacks in all AHP patients.

There was a corresponding 90% reduction in median annualize attack rates, with 50% of patients achieving attack – being attack free from porphyria attacks, all components of the composite attacks and our subgroup analysis showed consistent effects favoring givosiran. Givosiran resulted in a mean reduction in days on hemin use of 77% compared to placebo. The data show overall safety and tolerability of givosiran was acceptable in AHP of serious disease with incredibly high disease burden.

The open-label extension data support maintenance of reduction and composite attack rates and urinary ALA levels again causal for the disease and the OLE period showed a consistent safety profile.

Here we show a number of presentations that summarize additional ENVISION results, that were presented at the International Congress of Porphyrins and Porphyrias this year at Milan, Italy. These studies show effects of givosiran on patient reported outcomes, and other data. These results can be found on the Capella section on the company's website.

Akin Akinc

Vice President & General Manager-Fitusiran, Alnylam Pharmaceuticals, Inc.

Thank you, Jae. Now, I'd like to just switch gears a little bit and provide a bit of context for the opportunity that we have in front of us to make a difference for patients with AHP and also describe our efforts to support disease, awareness and diagnostic education efforts.

First of all, let's just start with the fact that AHP is a devastating disease. It's characterized by severe pain, potentially life threatening attacks and significantly reduced quality of life for patients. Furthermore the onset and progression of attacks, as well as the overall progression of the disease course can be very unpredictable, which in and of itself is a source of fear and anxiety for patients.

And as you can see, I just want to talk a little bit about the pain. You focus on the quote on the left hand side just read one of them. The pain is all consuming. I mean it's like someone holding, squeezing, stabbing. You're not able to function. You can't do anything. You just want to die. So the pain in porphyria really is something unique and it has been described as something that is incompatible with life.

So the significant humanistic burden of AHP is also accompanied by a very significant economic burden as well. We've done an analysis of the average annual healthcare expenditure from the EXPLORE Natural History Study. Really the cost drivers in AHP come down to three components, there's a treatment which Dr. Nagalla described hemin, that can be used for acute attacks. There is also hemin that's used prophylactically. And finally there are costs associated with the hospitalizations and emergency department visits.

And when we do an analysis of the results from the EXPLORE Natural History Study, we see that the costs can range from $400,000 a year, in terms of hospital costs, whereas if we look at hospital charges that can go as high as $650,000 a year, so very significant economic burden for these patients as well.

Now, if we look at the patients that are affected, this is a disease that affects primarily women and primarily people who are really in the prime of their life, either individuals who are attending school, pursuing their careers and raising families, so it's a disease that has a dramatic impact not only on the patients, but also on the people, in the lives of these patients as well.

The consensus estimated global prevalence of AHP is in the range of two to five per 100,000 for people with symptomatic disease. And it's been estimated that there are around a 1,000 who are severely affected with

recurrent attacks in the United States and Europe. And of course, many more estimated to have more sporadic attacks, and yet additional patients likely have chronic symptoms and impaired quality of life.

AHPs are challenging to diagnose, and so many patients with active disease are remaining undiagnosed. In our internal – however, our internal estimates suggest that there are around 3,000 patients with active disease, who are currently diagnosed in the US and Europe with around a 1,000 who are in the most urgent need with frequent attacks.

As has been described, it's often a long, frustrating journey to diagnosis and patients can remain undiagnosed for up to 15 years. And this can result in multiple hospitalizations, often unnecessary surgeries, and multiple misdiagnoses along the way.

But clearly, there is significant opportunity to improve awareness and diagnosis in this disease, and I just wanted to describe that we're doing – at Alnylam, we're doing what we can to help support the excellent efforts that are ongoing with the various patient advocacy organizations and physician communities that care for and treat these patients. We have educational initiatives that we've kicked off that are both tailored to the physician community as well as to the patient community.

And also we have instituted the Alnylam Act Program in acute hepatic porphyria. This is our no-charge, third-party led genetic testing and counseling program. This is available in the United States and Canada and the tests and services are all performed by independent third parties.

And so far as a part of this program we've had over 500 samples submitted and have seen to date over 50 positive AHP mutations that have been identified.

In addition we're thinking creatively about how we can reach patients, potential patients, and we know that folks in this community, particularly in this demographic are online they are participating in social media looking to connect with others who might have the symptoms they have looking for information. This is just one of these efforts that are described on this slide looking at Facebook health communities, where we can target online health surveys, individuals who are looking for information can respond to those surveys, and based on their responses have additional information that's provided. Finally, they can opt in to be contacted for further information about AHP.

So far we've had roughly 17,000 individuals who've completed the initial survey, 70% of them have described intense abdominal pain that required them to seek emergency or urgent medical care. And interestingly, 90% mentioned that it has reoccurred without a proper diagnosis and treatment.

And on the right hand side, which you can see is part of survey when we ask about other symptoms that have been experienced along with the excruciating abdominal pain, we see some very interesting symptoms here in terms of seizures, skin sensitivity, reddish brown urine color that all are at least consistent with AHP. So again, this might be one way of potentially reaching more patients where we could deliver additional information about AHP.

In addition, what we have announced August of this year a collaboration with Ironwood Pharmaceuticals that we're very excited about. This is a US focused Gastroenterologist Disease Awareness and Promotional Agreement. As Dr. Nagalla had described due to the many GI manifestations of AHP, gastroenterologists are one of the most frequently seen specialty groups during the diagnostic journey of a patient.

Through our research, we've found that around 20% of AHP patients receive their diagnosis from a gastroenterologist, even though overall awareness among gastroenterologist of the disease is quite low. And diagnosed patients typically see three or more gastroenterologists during their journey, with 40% of AHP patients receiving a prior diagnosis of IBS.

But just to provide an overview of this agreement, Ironwood will provide disease education to gastroenterologists to support accurate diagnosis of AHP patients. And we really see Ironwood as a premier partner here who have quite a reach and a very experienced sales team and deep relationships in this community. And if givosiran is approved, Ironwood clinical sales specialists would then begin promotional efforts.

With just providing a little bit on the status and path forward for the givosiran program, the givosiran new drug application and marketing authorization applications have been accepted by the FDA and EMA respectively, givosiran has been granted priority review by the FDA with a PDUFA date set for February 4, 2020. There are potential additional approvals in front of us in 2020 starting in Europe. And then in 2021 and beyond, there could be potential approvals in Japan and rest of world.

And with that, I just want to say thank you to everyone who has listened in on this roundtable and will now move to a Q&A session.

Christine Regan Lindenboom
Vice President-Investor Relations & Corporate Communications, Alnylam Pharmaceuticals, Inc.

Thanks again. We'll now open it up for Q&A. As a reminder, please submit your questions by typing your question in the Ask A Question field and hitting send.

QUESTION AND ANSWER SECTION

Akin Akinc
Vice President & General Manager-Fitusiran, Alnylam Pharmaceuticals, Inc.

A

Okay. I think maybe we'll first start with a question for Dr. Nagalla. And the first question is, in your experience, what have been the biggest obstacles to accurate AHP diagnosis and how might this change in the future?

Srikanth Nagalla
Program Director, Hematology Oncology Fellowship Program, Harold C. Simmons Comprehensive Cancer Center

A

So, as I mentioned, the first thing is the diagnosis, right, because patients are presenting with non-specific symptoms and signs and they're going to different specialists and each one is looking at their part, but porphyria is always an afterthought. So I think what was just described is great, just increased awareness of the physicians about the disease would be something that we have to do from that standpoint.

Now, part of the reason is, there were not many good treatment options other than hemin patients don't have many options, and hemin is very difficult for everybody to give. So, that could be one of the reasons why a disease is not – that people don't become very aware of a disease.

Now, when you make effective treatment for a disease that could change, because now they know that they have a drug that is very effective and much more easy to administer, so that automatically can also help awareness.

The second part is diagnosis in terms of the labs. So again, people order the wrong labs. They don't order the PBG or ALA initially. And again, that's going to change as we educate them and increase the awareness and also one other way to clinch the diagnosis is genetics, so again that's becoming very prevalent. So in the future, once we have effective therapies like givosiran, that's definitely going to help the both diagnosis and the management of these patients.

Akin Akinc
Vice President & General Manager-Fitusiran, Alnylam Pharmaceuticals, Inc.

A

Okay. Thank you. Maybe another one for you Dr. Nagalla, is a question here. How do AHP patients typically find their way to you? Are they referred to by other specialty groups?

Srikanth Nagalla
Program Director, Hematology Oncology Fellowship Program, Harold C. Simmons Comprehensive Cancer Center

A

Yes. So, I am a hematologist. And I might be the last one, but most patients do come to me in the end, because they have gone to different specialists, but as was mentioned gastroenterologist is somebody who sees these patients very often. Of course, they end up in emergency room very often.

And then, as people exhaust all the diagnoses and patients have had other interventions, and nothing is coming out of it, finally, somebody might pick up a book and go through all the differential diagnosis and say, oh, this could be porphyria. And that's how they end up, because mostly in the United States, porphyrias are treated by hematologists/oncologists, but mainly hematologists, because it's a disorder of heme, so people think that a hematologist is the right person to deal with that.

But again, that could change in the future with the advent of drug like givosiran, where primary care physicians in the United States might be comfortable taking care of them or even gastroenterologists and hepatologists who would be doing more of this.

Yeah. So, I come in little bit late in the thing or people kind of call me and ask me, what's going on. I say, it could be porphyria. And then, they say, okay, why don't you do the right workup and take care of the patient. So, that's how I get involved.

Akin Akinc
Vice President & General Manager-Fitusiran, Alnylam Pharmaceuticals, Inc.

A

Great. Thank you. Next question, I guess, I will direct that to Jae. Jae, can you speak some of the secondary endpoints that weren't significant? In particular, maybe talk a little bit about pain and thoughts on why?

Jae B. Kim
Vice President-Clinical Development, Alnylam Pharmaceuticals, Inc.

A

Sure, Akin, thank you. So, maybe it's worthwhile starting that most of the symptom-related PR, patient reported outcomes were single-item worst symptom instruments. And usually, these require several hundred patients to be treated to even show modest change. And we were actually incredibly impressed with the impact the pain symptom daily worse pain in acute intermittent porphyria results.

The pre-specified analysis towards that pain endpoint was initially had assumed a normal distribution in the effects on change from baseline, and which I think in retrospect was not a great assumption, because typically

these type of endpoints are not normally distributed. So according to our analysis plan, we could use what it's called a nonparametric approach or one that does not assume a normal distribution [ph] in the effect (00:47:58).

And when the appropriate statistical method is applied, we actually met a nominal significance of p-value of 0.04 effect on pain, also lending a great deal of reassurance that this observation is true is that if the mean effects on change from baseline in the pain instrument, over time there was a clear separation of impacts the pain with givosiran treatment compared to placebo.

Also notable is the effect on the physical component summary of the general symptom instrument SF-12, or Short Form 12, here we show a nominal p-value of 0.02, and again I speak the nominal significance, because the sequential testing procedure stopped at the mean composite attack rate in AHP as we see in slide number 29; but yeah, so again, it's – we are actually incredibly impressed with our impact on the symptoms with givosiran treatment and I think the fact that we see anything at all with the study of this size is truly impressive.

Akin Akinc
Vice President & General Manager-Fitusiran, Alnylam Pharmaceuticals, Inc.

A

Great. Thank you, Jae. Another one that I'll send your way Jae, we have a question that's come in. Do you have a hypothesis or understanding of how CKD develop in the patients in the givosiran group?

Jae B. Kim
Vice President-Clinical Development, Alnylam Pharmaceuticals, Inc.

A

Sure. Maybe first worth clarifying that CKD is really a very common comorbidity with acute hepatic porphyria and it was present in most patients who were enrolled in the trial. The nature of that CKD is really manifold and it related with AHP by virtue of likely vascular dysregulation from the neurotoxic heme intermediates. What speaks to this is also the common prevalence of hypertension in this population and also hypertensive events in these populations that these patients experience. So at a high level, I think one, kidney disease is really goes hand-in-hand with acute hepatic porphyria and what we show with patients who are treated with givosiran, they show a small and transient change in serum creatinine that either stabilize or normalize with continued givosiran treatment and also a purely hypothetical mechanism is that perhaps in patients with constant vascular dysregulation and hypertension treatment that reverses that to some extent might also be expected to cause a slight and transient bump in creatinine; so a purely hypothetical point in that.

Akin Akinc
Vice President & General Manager-Fitusiran, Alnylam Pharmaceuticals, Inc.

A

Thanks, Jae. Another question maybe that I'll direct to Dr. Nagalla. What type of chronic symptoms do you usually see in your patients and how do these symptoms impact the everyday lives of your patients?

Srikanth Nagalla
Program Director, Hematology Oncology Fellowship Program, Harold C. Simmons Comprehensive Cancer Center

A

Thanks. So, most of the times, it's these chronic neuropathies and abdominal pain. So it's kind of really debilitating because we think we talk about this acute attack, but in between these acute attacks, a lot of patients, they never normalize, the symptoms never normalize. They continue at some degree. Now it may not be 10 out of 10 pain, but it's always the 5 out 10 pain. So there's always this anxiety or that is there is this worry that they might have the next attack. So it's mentally and physically both affecting the patients with a day-to-day activity. So, one of this – one of the thing as you just mentioned is the pain component, the next is the psychological component. And then what happens over a period of time is nerves get damaged. Due to this recurrent attacks,

patients start getting peripheral neuropathy, so that becomes a problem and it's a challenge. It's painful and they're not able to do their day-to-day activities just because of the neuropathy. And of course we just spoke about the kidney disease and then patients going on dialysis.

The other component of this could be just the high blood pressure requiring lot of medications. So these are all some of the very common things that we see on a day-to-day basis. But again, seizures like recurrent seizures sometimes could be there, they need to be on anti-seizure medications. They need to watch what they eat; so they have to make sure that they eat enough carbs, that they take away the triggering factors. So they just have to pay attention to so many components, it's almost like walking on eggshells just because they don't know what's going to trigger their next attack. Thank you.

Akin Akinc
Vice President & General Manager-Fitusiran, Alnylam Pharmaceuticals, Inc.

A

Thank you. Next question is how challenging is it to reach the diagnosed population? How well connected is a diagnosed community and what differentiates the 3,000 diagnosed from the 1,000 with high need and maybe I'll take that one. I think some of the challenges have been described. For the diagnosed population, however, these are individuals who fortunately we have very good patient advocacy organizations available, particularly in the United States and many of these diagnosed patients are connected through the American Porphyria Foundation. So I think that's a great outlet for being able to reach this community. However, I think one of the challenges is that many of these patients who are diagnosed, not all of them have had a very good experience with the healthcare system. Given a kind of long diagnostic journey, we hear multiple cases where people have thought that this was all in their head, they've been labeled as drug seekers. And so as a result of that, we know there is a significant fraction of the diagnosed community who is a little bit suspect of the healthcare system. So clearly, that is a challenge. However, we're hopeful that if there is a new therapeutic option for patients that works, that's a chance to reset a new relationship with the healthcare system.

Now in terms of the 3,000 that are diagnosed, that have active disease and the 1,000 – you know I think the greatest differentiator there is just the frequency at which they are – the frequency and severity of the symptoms that these patients are experiencing. Obviously the 1,000 who have frequent recurrent attacks, they're interacting with the healthcare system much more frequently in terms of coming in to the emergency department or being hospitalized and being treated with hemin. So those are the folks who have the most urgent highest unmet need today and that will really be assuming approval for givosiran, that will be our initial focus and then we'll proceed from there.

And I think we have one more time for one last question and that last question is how will you leverage your commercial infrastructure for givosiran's launch and is additional build-out needed? Again, I think I'll take that one. Fortunately, much of the commercial capability is already in place that we've had to build for the ONPATTRO launch last year and we're now in a great position to leverage a lot of that for givosiran. So that includes the access functions such as our patient support program Alnylam Assist, as well as the disease education capabilities that are managed by our medical affairs team. So we will be making some incremental addition to the field force to address some additional call points that are specific for givosiran. But again we're very much looking to leverage the infrastructure that's been built for ONPATTRO.

So I think with that, we're going to close and I'll hand it back to Christine.

Christine Regan Lindenboom

Vice President-Investor Relations & Corporate Communications, Alnylam Pharmaceuticals, Inc.

Great. Thanks Akin and thanks for the rest of our speakers as well. This concludes our RNAi Roundtable for today. The replay and slides will be posted on the Capella section of the Alnylam website later today at alnylam.com/capella with the transcript to follow shortly thereafter. We hope you could join us for our next RNAi Roundtable this coming Thursday October 10 at 11:30 AM Eastern Time as we discuss lumasiran in development for the treatment of primary hyperoxaluria type 1. For those details, please visit www.alnylam.capella (sic) [www.alnylam.com/capella] (00:58:16). Thanks everyone and have a great day.