THOMSON REUTERS STREETEVENTS

EDITED TRANSCRIPT

ALNY - 2018 RNAi Roundtable: Givosiran, in Development for the Treatment of Acute Hepatic Porphyrias

EVENT DATE/TIME: JULY 24, 2018 / 2:00PM GMT

CORPORATE PARTICIPANTS

Akin Akinc *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Hemophilia Program*

Christine Regan Lindenboom *Alnylam Pharmaceuticals, Inc. - VP of IR & Communications*

Jae Kim *Alnylam Pharmaceuticals, Inc. - VP of Clinical Development*

PRESENTATION

Christine Regan Lindenboom - *Alnylam Pharmaceuticals, Inc. - VP of IR & Communications*

Good morning, everyone. Thank you for joining us for today's RNAi Roundtable, where we'll be discussing givosiran and development for the treatment of acute hepatic porphyrias. 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 Mary, a patient living with acute intermittent porphyria. Unfortunately, Dr. Eliane Sardh of the Karolinska in Sweden, who was originally scheduled to participate in today's roundtable, will not be able to join us due to a last-minute conflict. We are pleased that Jae is able to step in on short notice.

Today's RNA Roundtable is a second in a series of roundtables that we are hosting this summer. Today's event is expect to run for 1 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'll 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'll turn it over to Akin.

Akin Akinc - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Hemophilia Program*

Thanks, Christine. I'm going to first start by a brief introduction, and then I'll hand it off to Jae. For those who have followed the Alnylam story, you know that we've been working to develop therapeutics based on RNA interference or RNAi, which we believe are going to form a new class of innovative medicines. This technology is founded on Nobel Prize-winning science, and it allows us in theory to silence any gene in the genome using a potent and durable natural mechanism of action. Using RNAi, we've built a product engine for sustainable products, and we're now at a very exciting point in our country's -- in our company's evolution, where we're now entering commercial stage.

On the next slide here, you can see Alnylam's clinical development pipeline. You can see that we have a pipeline focused in very strategic therapeutic areas, with the majority of programs in the genetic medicines. Our lead program, patisiran, for the treatment of hereditary ATTR amyloidosis, is in registration, and we're eagerly awaiting approval sometime this summer. What we're going to be talking about today is givosiran, our program in the acute hepatic porphyrias, a program for which we have Breakthrough Designation and which we are currently in Phase III clinical studies.

I'm now just going to give a little bit of background on the rationale for givosiran as an RNAi therapeutic. Givosiran targets ALA Synthase 1 or ALAS1, which is a liver expressed enzyme. It's the initial enzyme of the heme biosynthesis pathway, the pathway which contains the defects that are responsible in acute hepatic porphyrias, and Jae will speak more about that. Up regulation of ALAS1 results in accumulation of toxic heme intermediates. And by down modulating ALAS1, we can reduce the accumulation of those intermediates. Now again, we have in this program biomarkers, which we can readily follow in the serum and urine, notably ALA and PBG. And in this program, we have a single pivotal study in acute hepatic porphyria patients, where we have clear endpoints which we can follow. And again, Jae will speak more about that.

So with that, I'll hand it over to Jae.

Jae Kim - *Alnylam Pharmaceuticals, Inc. - VP of Clinical Development*

Thank you, Akin. It is my distinct pleasure to share with you an encore of the presentation from Professor Eliane Sardh's abstract presentation at the European Association for the Study of the Liver Congress in April of this year. Here, we illustrate an overview of the disease. Acute hepatic porphyrias are inborn errors of heme synthesis from liver enzyme defects. On the right-hand panel, you see kind of the metabolic pathway in the synthesis of heme in the body, specifically in the liver. And central to this path is the induction of an enzyme called aminolevulinic acid synthase 1. And in combination with the induction of this pathway with loss of function mutations in enzymes along that pathway leads to the buildup of toxic heme intermediates, principally aminolevulinic acid or we'll refer to it as ALA or porphobilinogen or PBG. The pathophysiology of this disease is that the buildup of ALA and PBG leads to the symptoms and clinical sequelae, which are both attacks of porphyria and also chronic manifestations, which we will go into detail a little bit later. Really, the attacks are described as excruciating pain that can be in the abdomen or in the back, and they're called acute neurovisceral attacks, and they can be life-threatening. There's also chronic pain and discomfort, which we'll describe a little bit later as well. And there's also a high prevalence of anxiety, depression and disability, and social isolation is common as a result of these symptoms.

Next slide, please. We're on Slide #12. As described, heme intermediates are circulating neurotoxins, and they result in protein effects across the nervous system and the body. Here, we list some of the characteristics of acute neurovisceral crises that result from porphyria. They include autonomic neuropathy, which leads to excruciating abdominal pain, nausea, vomiting and as well tachycardia, cardiac arrhythmias, labile hypertension and sweating and so forth. There's also acute peripheral neuropathies. They can lead to diffuse muscle weakness, pain across their backs and limbs, neuropathic sensory loss and cranial neuropathy. There is also central nervous system manifestations that include numerous mental symptoms and potentially acute encephalopathies, headaches, somnolence and even seizures. There's also a number of metabolic manifestations of this disease as well. Next slide, please.

Alnylam embarked on the characterization of these patients who have repeated attacks in a natural history study called EXPLORE. And here, we illustrate some of the patient-reported chronic symptoms. They're reported in addition to the acute attacks. Here, 65% of these patients reported chronic symptoms in between their attacks, which are most commonly reported as pain, tiredness, anxiety and nausea, with these symptoms occurring in 46% of those reporting -- of those patients reporting chronic symptoms, 46% report having these on a daily basis. Next slide, please.

The EXPLORE Natural History Study also evaluated quality of life in this debilitating disease. And here, we show that across health status domains, there were numerous -- a great proportion of patients who were reporting disability in these domains. And the health domains that were most markedly impacted were those of usual activities, pain and discomfort and anxiety and depression. And it's notable that these domains are not impacted by whether patients use hemin prophylaxis or not. Next slide, please.

As we have discussed before, pain is a key characteristic of the symptom of this disease, and in the EXPLORE Natural History Study, there was a further exploration of these pain characteristics. It is notable that pain -- chronic pain was reported 3.5 intensity out of 10 on a scale of 10 in patients in between attacks, and this increased during attacks to 6.4 out of 10. And the pain that is reported in between attacks persists at even assessed in month 6 and month 12, again, irrespective of whether or not patients are treated with hemin intravenously, used prophylactically and/or use of opiates. Next slide, please.

Here, we illustrate the therapeutic hypothesis for givosiran, which is, as Akin had mentioned, an investigational RNAi therapeutic intended for the treatment of acute hepatic porphyrias. The therapeutic hypothesis is rooted in that the induction of ALAS1 leads to the synthesis of heme intermediates, principally ALA that induce porphyria symptoms. And givosiran, by reducing or knocking down the ALAS1 protein, results in lowered ALA and PBG, which are causal for the symptoms of the disease. Next slide, please.

Here, we illustrate the schematic of the Phase I and open-label extension study design. And in the upper portion of the slide, we show the Parts A and B of the Phase I study, which were a single ascending dose and multiple ascending dose portions of the trial. It was conducted in a population called chronic high excreters, which are patients who have the mutation for the disease, and they have high levels of a causal biomarkers, but they do not yet have attacks. And this is a generally clinically stable population in which we can study the natural history of single and ascending dose studies for the clinical pharmacology portion of the study. Urine, ALA and PBG could be evaluated over time. The following portion of the Phase I study in Part C was after the dose escalation portion. The investigational agent, givosiran, was studied in patients with recurrent attacks to evaluate clinical activity. And these patients also were rolled over into an open-label extension portion of the study where ongoing givosiran therapy can be evaluated for long-term efficacy and safety. Next slide, please.

The demographics and baseline characteristics of this Phase I study show that we recruited the intended population of patients who have acute intermittent porphyria, and they were principally female. And as we discussed before that porphyria is a disease primarily that affects women, and interestingly, one of the principal causes of these attacks are menses. And here, you can see here that some of these patients were taking, for example, a GnRH analogue use, and that is one therapeutic modality where you actually induce a menopause in women in order to reduce symptomatology of the disease. I mean, we're hopeful that we would in the next generation of therapeutics for this disease run through these therapies in the past, archaic in the way that we would use phlebotomy, perhaps. But half of these patients are also on human prophylaxis, and a good number of these patients are chronically taking opiates to treat their pain. We also reassuringly found that these patients had induction of ALAS1 mRNA as we had expected with the resulting elevations in ALA and PBG, which, again, we said are causal neurotoxins in this disease. Next slide.

Here, we summarize the safety and tolerability in the Phase I study results. We show that most -- as typical in Phase I studies, most patients reported adverse events irrespective of their treatment assignment. We do summarize that there were 6 patients who had serious adverse events, but none of them were assessed as related to study drug for the investigator. In Part A, 2 patients had abdominal pain that required hospitalization, and there were self-limiting results. In Part B, there was 1 patient who had pregnancy. The conception was approximately 3 months after the last dose and had resulted in a miscarriage. And in Part C, 3 patients reported SAEs. One patient had opioid bowel dysfunction. One patient had influenza. And one patient had bacteremia from a portacath that resulted in a number of complex sequelae, and she was also quadriplegic from her antecedent frequent attacks. And her complicated history had resulted in hemorrhagic pancreatitis, which was a fatal outcome. And the evaluation led to an assessment that this SAE was unlikely related to study drug due to the antecedent -- due to the presence of gallbladder sludge, which was previously reported. There were no other discontinuations to adverse events or other clinically significant changes in ECG, clinical laboratory, physical examination. And review of adverse events reveals no clear relationship to dose. Next slide, please.

Here, we illustrate really the central clinical pharmacology of this -- of givosiran, is that givosiran led -- treatment led to durable ALAS1 mRNA silencing. And here, we show that approximately 60% to 70% of ALAS mRNA is silenced, especially with monthly dosing. Next slide, please.

Here, we evaluate the impact of givosiran-induced ALAS1 reduction on lowering of ALA and PBG. Here, we show the results in the Phase I Part C population in recurrent attack patients, and I remind you again that these are patients with induced ALAS1 with very high levels of ALA and PBG. On the left-hand panel, we show urinary ALA levels. On the right-hand panel, urinary PBG levels. And monthly dosing led to consistent and sustained lowering of ALA and PBG to greater than 80%. And one thing we do note, and you see this very stable solid line in the 2.5 milligram per kg monthly and 5.0 milligram per kilogram monthly. And we show that increasing their monthly does from 2.5 to 5 milligram per kilogram did not result in any further lowering of ALA or PBG. Next slide, please.

Here, we show the impact of the lowered ALA and PBG on clinical activity, principally on the impact on annualized attack rates and decreased intravenous hemin use. On the left-hand panel is -- illustrates annualized attack rate and with the Y axis mean annualized attack rate. On the right-hand panel, also the mean annual hemin doses. And we show that monthly dosing led to greater mean reductions in annualized attack rate up to 83% reduction and annualized hemin use up to 88% relative to placebo. And we also show that an increase in dose from 2.5 to 5 milligram per kg on a monthly basis did not substantially improve the clinical activity in the drug. For this reason, we have selected 2.5 milligrams per kilogram monthly as the go-forward regimen for further investigation. Next slide, please.

Here, we show the association of annualized attack rates with aminolevulinic acid lowering. And in response, in the X-axis, we show the quartiles of ALA lowering corresponding to the annualized attack rates, and we show a continuous relationship between annualized attack rate and ALA lowering, really reinforcing the therapeutic hypothesis that ALA is causal for annualized attack rate and also modifying or lowering ALA to reduce attacks and result in improved clinical activity. Next slide, please.

Here, we illustrate the -- or summarize the safety and tolerability from the open-label extension study, and many patients reported adverse events. Two patients reported SAEs. One patient had an upper extremity DVT, assessed as unlikely related to study drug due to prior indwelling central venous catheter and venous damage from chronic hemin usage. And one patient had an anaphylactic reaction, assessed as definitely related to study drug. This patient had an antecedent history of pronounced atopy or history of asthma, oral allergy syndrome and prior allergic reactions to acne cream and possibly latex gloves. The anaphylactic reaction occurred after the third dose, and the patient symptoms resolved with medical management and patient discontinued from the study. There were adverse events in -- that were reported greater -- and greater than 3 patients

included abdominal pain, nausea, injection site erythema, headache, pruritus, fatigue and nasopharyngitis. There were no clinical significant increases in LFTs or lipase with ongoing dosing and open-label extension studies. Next slide, please.

Here, we summarize the clinical activity in the open-label extension study. And what's highly reassuring is that with extended dosing in open-label study, clinical activity is maintained. The mean time in the open-label extension study was 10.6 months, with up to 22 months of total treatment in Phase I and open-label extensions. Continuous dosing at 2.5 milligrams per kg monthly resulted in potentially enhanced clinical activity. ALA and PBG lowering was sustained at greater than 80%, and mean reductions of annualized attack rate of 93% and 94% in annualized hemin use was observed in the open-label extension relative to the Phase I run-in. 42% of patients or 5 out of 12 reported an annualized attack rate of 0 for a mean of 7.4 months. Next slide, please.

The therapeutic hypothesis clinical activity can also be evaluated in those patients who are in Phase I assigned to placebo who crossed over into the open-label extension. It's kind of a second shot on goal for a randomized study as a move to the extension portion of the study. So here, patients who had previously been randomized placebo who crossed over into givosiran showed a reassuringly remarkable reduction in attack rate and hemin use as they crossed over into givosiran treatment and open-label extension. Two out of 4 of these placebo patients who went on to givosiran reported an annualized attack rate of 0 for a mean of 11.2 months. Next slide, please.

In summary, the Phase I study showed that givosiran lowered induced ALAS1 with corresponding reductions in both ALA and PBG, which are the causal neurotoxins in this disease, and reduced attacks and hemin use in recurrent attack patients. The dose regimen of 2.5 milligram per kg monthly was selected for further clinical development, and interim open-label extension study results demonstrated maintenance and potential enhancement of clinical activity with continuous monthly dosing. The clinical activity and safety profile support continued clinical development, and our pivotal Phase III study named ENVISION is ongoing and enrolling patients. Thank you.

Akin Akinc - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Hemophilia Program*

Thank you, Jae. Now it's my pleasure to hand the call off to Mary, who is going to provide us with her perspective of living within acute hepatic porphyria. Mary?

Unidentified Participant

Hi. This is Mary. And as you can see from my pictures, I was a perfectly healthy child and teenager and young adult, went through college with absolutely no disease activity. I then began my career in international business, bought my own house at 25, and my life was looking great. Unbeknownst to me, I had this sleeping dragon, as we call it the purple dragon, hiding in my system. And something as simple as an ear infection completely turned my life upside down. When I was 28 years old, I was given a sulfonamide antibiotic for an ear infection. And on the fifth day, my fiancé came home and found me passed out. That started my long and painful diagnostic journey. The symptoms of porphyria are varied and looked like so many other diseases that -- and it's so rare that doctors don't even really look for porphyria.

So over the next 18 months, I had 12 attacks, most of which put me in the hospital. All of which sent me at least to the ER. Had every test under the sun done: MRIs, CAT scans, different probes and GIs, blood and urine. Eventually, was even sent for a psych eval because when all your tests show you as being perfectly healthy, they start to question if it could be hypochondria. I knew it was real because the pain was undescribable. It's so bad that you'll crawl to the bathroom, and when you're done, you'll just lay on the floor because it hurts too bad to crawl back to your bedroom. So finally, during my 12th attack, I was in ER, and I had given a urine sample. One of the things with porphyria is when the signs can be a port red-colored urine and a doctor made a joke about the nurses drinking wine out of urine sample cups. And this was not my doctor, just a doctor passing through made this joke, and I yelled out into the hallway that, that was mine. The doctor came into my room and flipped through my file and was holding the urine cup up to the light like he had never seen anything like this before. And after asking a few questions, he finally said, "Have you heard of porphyria?" And I said, "No." And he said, "Well, I really hadn't either, but I saw a movie 3 nights ago that discussed this very thing and the red wine urine. I think we need to test you for that." So the tests were done, and I was positive for porphyria. Being diagnosed in 18 months, I was actually one of the very lucky ones, and just a fluke that, that doctor walked through the ER at the moment he did. Because many patients will go 10, 12 years on their journey to a diagnosis.

Let's see. Over time, well, with my -- when the disease first started, I was having attacks every single month, every 28 days. It had clicked into my menstrual cycle, which happens to a lot of women with porphyria. But over time, because of the disease, because of the medications used, I went chronic. So as in the past where I'd be sick 2 to 3 weeks of every month and be hospitalized, I would have 1 good week every month, and that was a lot. That was great. Now every day of my life, I feel like I have a really bad flu, the abdominal pain, the nausea, the vomiting, the all-over body aches, bone pain. And on top of that, I also get the acute attacks if something triggers me, a medication or fasting. There's many things that can trigger it. So I'm now both. I'm acute and chronic. I have also, 12 years ago in a very bad attack, had full body paralysis, including respiratory arrest. Everything came back except my radial nerve. So to this day, my hands and wrists are paralyzed from the disease, and nobody knows if this is a permanent thing or if it's something because of all the toxins that are in my body.

Right now, there's really, in my mind, no treatment for porphyria. And by that, I mean, there's nothing that can stop me from having an attack. I've tried different things. I've tried hematin prophylactically, once a week, once a month, 4 times a month in every combination possible, and that did nothing. I tried the GnRh hormonal analogue that was spoken of earlier. That did nothing for me except cause early and permanent menopause. So really, all we have right now is hemin, which to me is a dangerous primitive Band-Aid. We get sick, then we're given the medicine. And then we may already have permanent damage like the paralysis or other things. It also has a dangerous method of delivery being through ports. So for myself, I've gone through 6 ports, had one broke in my body, had pseudomonas sepsis in one, had septicemia in another and then had 3 others get clogged. I know some women who've had over a dozen ports. Every time you're doing a surgery like that, you have risk of infection. So it's just not a good way of delivering in a drug.

Having gone chronic with this disease, my life is now -- it used to be the whole wide world and traveling to almost 40 countries, skiing, bike riding other countries, caving. Now my life is my bedroom. It's a very isolating difficult disease because nobody understands what you're going through when it comes to these invisible rare diseases. It's not like cancer that if you say you have cancer, everyone understands. You say porphyria, they don't know what it is. It's hard to describe, and it -- I don't even know how to say it, but people just react differently when they don't know what it is. They think you could be contagious, or they believe it's not really as bad as what you're saying because nobody really sees us when we're that sick. So it's very isolating. I've talked to other porphyrics about this, and so many of us, we've lost so many friends because you can only turn them down so many times before your friends stop calling. You don't want to be a Debbie Downer, but it's hard to always be there for your friends and maintain a positive attitude when you're hurting so badly. So it's that isolation, that kind of disengagement from your social life and your hobbies, even not working and being on disability as an adult just leaves you so isolated and alone. And so there's aspects of depression that come in with that because you're not out there with your friends. You're not being an active member of society like you've been for so long.

I know that myself and all the other porphyrics that I know and that I work with, we're just desperate for a medicine in the future that will prevent these attacks before they happen that we don't have to wait until we're so sick that we're crawling into ER to be treated. Anything that can stop them before happening will be just a lifeline to us. If we didn't live with the fear that we have every day, I think it would do a lot just to kind of restore our life and our hope, our -- we'd be more likely to make plans because we all think we can make it rather than now, someone asks me to do something, I'm like, "I don't know if I'll be sick in a week, so I'll let you know." So really, the idea that everyone is praying for and begging for is a medicine that will stop these attacks before they ever happen, and that I think could possibly give me my life back.

So thank you for listening to me and wanting to learn about this disease.

Akin Akinc - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Hemophilia Program*

Wow. Thank you, Mary, for sharing your story with us. I now have the unenviable task of following Mary to talk a little bit about the opportunity for the program as we see it as well as providing an update on the program status.

So I think, first of all, as we think about the program opportunity, it's really addressing all the things that Mary described. I think that's what -- clearly, there's a huge unmet need. There are patients who are suffering from this devastating disease who really have very limited options, and I think that for us is really truly the opportunity that we're pursuing.

Now in terms of the patient population, just a little bit of descriptor on that. Consensus estimates for the prevalence of the disease globally are in the range 2 to 5 in 100,000. We've already heard that this is the predominantly female population, roughly 70% to 80% of the population being

female. And approximately 5% of those patients with AHP may be severely affected who have frequent recurrent attacks, and current estimates are in the range of approximately 1,000 patients with such recurrent attacks in the U.S. and in Europe. But we know that many more patients have sporadic attacks. And as we're learning more and more from talking to patients like Mary as well as some of the work that we've done with -- in EXPLORE, many patients also have chronic symptoms and significantly impaired quality of life between attacks. So we're learning more and more that this is a population where it's not just all about attacks, but there's lots of unmet need beyond the attacks. And finally, this is a patient population that is for the most part dealing with the high rate of an undiagnosed patient population. And that's because AHPs are really challenging to diagnose. In some sense, Mary was one of the lucky ones, as she said, getting a diagnosis in 18 months. But we know that for many patients, they suffer repeated misdiagnosis and often lengthy delays in diagnosis that can last up to 15 years. And really, the challenges are not uncommon with rare diseases with low awareness. But this disease also has the added challenges of being highly variable in its expression and coming with a constellation of nonspecific symptoms with a high degree of overlap with other more common diseases. Next slide, please.

If we look at the treatment landscape, right now, there are no approved therapies for the prevention of attacks. Hemin is the only available therapy that's used for the treatment of acute attacks. It's not approved for prophylactic use, and that's due in large measure to the fact that it has a short duration of activity, with a half-life of around 11 hours. And that, coupled with the fact that it's given intravenously, really means that it's not ideally suited for prophylactic use. Nonetheless, given how desperate this patient population is, prophylactic therapy is attempted with hemin. But clearly, there is significant room for improvement in terms of efficacy. And in addition, as Mary pointed out, there are numerous side effects. Nausea, vomiting, headache, phlebitis are common. Because hemin is a blood product, it's a heme product, carries iron. With each dose of hemin, you also administer iron, so there's the risk of iron overload. And many patients need to have ports put in for the venous access, so there are venous disruption issues as well as complications arising from the use of a venous port.

So in addition to all the humanistic burdens of the disease that we've talked about, this is a disease that also carries a significant economic burden in terms of health care utilization and the cost to the system. And there's this data that we've shown previously from our EXPLORE Natural History Study looking at that patient population on an annual basis. And if we look at the costs for the hemin treatment used both acutely to treat attacks as well as prophylactically in some cases and then combine that with the costs or charges from hospitalization, we see an annualized burden, economic burden, ranging from $400,000 to $650,000 a year. Next slide, please.

So clearly, there are significant opportunities for improving patient care in AHPs, and that's really going to start with facilitating patient identification. And there's a long list of things that we're going to be working on to do our part, but clearly, we're not going to do all of this ourselves. We're going to do this in partnership with others in the community. I think the first step as a typical in rare disease really starts with increasing disease awareness and knowledge of the disease. Again, this is something that we work with others. There are excellent patient advocacy groups out there. And in particular, in the United States, there's the American Porphyria Foundation, who does a tremendous job raising disease awareness and providing knowledge, connecting patients with the disease, and we work very closely with them. We're also learning and through our efforts and efforts of others about the chronicity of the disease, and so we feel very good about the contribution we've made there through studies like EXPLORE to show that this is a disease that's not just intermittent for all, that it's not just about attacks. Next step, importantly, is to get patients tested and diagnosed. Again, we're going to be working to help better define the disease, identify the red flags, help promote guidelines for testing. And importantly, I think we're learning that even when there is a suspicion of porphyria, many times, the right tests don't get ordered. So I think there's a significant need to help ensure that the right tests get ordered and interpreted correctly. It's also going to be improving care networks. Again, in the United States, there's a porphyria consortium that do a tremendous job. And in Europe, there is the European Porphyria Network or EPNET. We are collaborating with them to help support their work in providing those care networks. But we're also learning that there are areas where the coverage is thin, and so we're going to be working to help establish, in some cases, new care networks and centers of excellence. I think, importantly, we're going to have to work with the community to redefine expectations for the treatment of patients. For so long, it's been really about just trying to get through that next crisis. And we've heard from Mary and we know from others that the patients in this community are resilient, and they put up with a lot. And I think hopefully with a new therapeutic option, there will be a reassessment of what the expectations are for treatment, for improving quality of life and also who should be treated. And finally, access, of course, is an important consideration. And there, we'll be working to partner with payers to try to facilitate access. We view it as our job to help provide them with the data and evidence that they need. Then we'll also be working with them to try to share risk where we can through innovative structures, including considering the use of value-based agreements where it makes sense. Next slide.

This is just one program that we're very proud of, Alnylam Act, which we, this year, expanded to cover third-party genetic testing for acute hepatic porphyrias. We've had, so far, into the middle of this year 123 tests submitted and 16 positive samples already. So this is a program that we hope will help folks in the community get the diagnosis that they need. Next slide, please.

Just a couple of words about the ongoing ENVISION Phase III study. Jae alluded to the study as well. This is an ongoing study that's randomized, double-blind, placebo-controlled in patients with acute hepatic porphyrias. There will be roughly 75 patients in this study, ages 12 and above who have a diagnosis of acute hepatic porphyria. There will be a one-to-one randomization in this study, with half of the patients receiving givosiran at 2.5 milligram per kilogram given once monthly subcutaneously. And then the other half of patients will be randomized, receive placebo. We have numerous endpoints on the study. The primary endpoint being attacks requiring hospitalization, urgent care visit or home IV hemin use. And there are a number of secondary and exploratory endpoints. Some of them include the biomarkers of ALA and PBG, hemin utilization and a variety of symptoms and quality of life measures. After a 6-month double-blind period, patients will have the opportunity to enroll in an open-label extension phase, where all patients will receive givosiran. Now as part of this study, we've built in a plant interim analysis, which is planned to occur in the September time frame. Next slide, please.

And just to wrap up, in terms of the time lines. If that interim analysis is positive, we plan to file for accelerated approval by the end of this year, which would potentially allow for an approval middle of next year in 2019. We would then follow that with MAA filing based on the full complete ENVISION results, which could allow for approval in Europe in the 2020 time frame. And then we envision approvals following on after that in Japan and rest of world in 2021 and beyond.

So I think with that, I'll just wrap up just by saying, obviously, we're very excited about this program and what it could mean for Alnylam as a company with the possibility of 2 approvals in 2 years following on, hopefully, approval of patisiran this year. And of course, we're very excited by what this program could mean for patients.

So with that, I'll stop there. And I guess, we'll move on to the Q&A portion.

QUESTIONS AND ANSWERS

Christine Regan Lindenboom - *Alnylam Pharmaceuticals, Inc. - VP of IR & Communications*

Great. Thanks, Akin. We'll now open up the call for Q&A. As a reminder, please submit your question by typing the question in the Ask A Question field and then hitting send. And we'll just give that a minute for the questions to queue up, and we'll hand it off to Akin.

Akin Akinc - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Hemophilia Program*

Okay. I'll -- here's one question that I'll -- we'll start out with. There's a question about what triggers attacks. And we've heard a little bit about that from Jae and Mary and what are the role that ALA and PBG play there as well. So maybe I'll kick that off to Jae to tell us a little bit about what are some of the triggers for attacks.

Jae Kim - *Alnylam Pharmaceuticals, Inc. - VP of Clinical Development*

Good. Thanks, Akin. As we mentioned before, the pathophysiology of the disease is that the -- in the background of a mutation, a loss of function mutation in the heme synthetic pathway, induction of ALAS1 are kind of feeding the path that has a roadblock of these accumulation of neurotoxic intermediates. So the induction of ALAS1 can be caused by any number of stressors. That include, for example, the most common are menses or the menstrual cycle. Others include infection and low blood sugars and so forth. So the current treatments at this time include acute intravenous hemin, which because it feeds the pathway that results in heme by giving hemin the feedback regulation, it makes the pathway think that there's already product so that ALAS1 isn't induced anymore. The other is -- stressor includes menses. As I mentioned before, prematurely or chemically-inducing menopause through GnRH analogues is also a treatment, although albeit fairly symptomatic treatment. Others include because

low sugar can be a stressor during attacks and sometimes in between attacks, patients are treated with carbohydrate loads, in very sweet, either snacks or solutions, and intravenous high concentration sugars given through a central line is also given during acute attacks.

Akin Akinc - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Hemophilia Program*

Thanks, Jae. There's another question regarding the addressable patient population and how big could the market be. I think, and as we've said before, if we think about the near-term opportunity, we know there are roughly 1,000 to 1,500 patients globally who have frequent recurrent attacks. And obviously, those are patients who we see as a near-term addressable population. Longer term, if we think about the sources of growth, obviously, it's our belief that patients who have less frequent attacks still have significant high unmet need. So there's a considerably larger portion of patients who have more sporadic attacks but who may be suffering from chronic symptoms and impaired quality of life, and that would be one area for expansion. And then second, we know that this is a highly under diagnosed disease. So we expect that there's going to be considerable opportunity as we and others in the field work to improve the diagnosis of patients with AHPs.

I've got a question here for Mary. Mary, maybe you can talk a little bit about the predictability of your disease and the attacks. You mentioned timing relative to the menstrual cycle, but maybe you can tell us a little bit about how regular is your disease course. And do you know when attacks are coming? When they're going to be really bad versus when they're just bad? Maybe you can speak a little bit about that.

Unidentified Participant

When I was younger from about 28 to 34, my attacks were every 28 days. I mean, it clicked in with my cycle exactly. So I knew when it was coming. And for me, I have about a 3-, 4-, 5-day buildup. So my pain will start getting worse. My abdominal pain gets worse. Those first 3, 4 days feels like the worst flu you've ever had. And of course, I'm praying let this just be the flu, let it be the flu. But by day 4 or 5, it would be a full-blown attack, where I couldn't even take a sip of water without

(technical difficulty)

that up. Sitting up in bed would cause screaming and crying. And I broke a tooth about 2 months ago that needed a root canal, and I had no pain, and they didn't even need anesthesia. So I'm not a big baby. So when I say that porphyria is painful, it is painful. It's -- yes, you really -- one doctor who has it says the pain of porphyria is -- oh, what term did she use? Sorry, I'm drawing a blank. But -- oh, she says that porphyria pain is incompatible with life and that having a child without anesthesia does not hurt as bad as a porphyria attack. So when we feel one coming on, we're in an absolute state of terror as to how bad it could be. At this point now that I had early menopause, I can't really tell when attacks are going to come because mine aren't triggered by the hormones anymore. And sometimes, I can figure out what triggers them if I'm given a new medication. That's an easy one. But other times, I've gone into an attack, and we've had absolutely no clue, and we're never able to figure out what triggered me. But it's always for me the same progression, the days of super bad flu and then going to full-blown hospitalized attack.

Akin Akinc - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Hemophilia Program*

Thanks, Mary.

Unidentified Participant

Yes. Oh -- and can I just -- sorry, can I just say something on the last question about how big the -- your patient population is going to be? That there was just that paper that Puy put out in France saying that 1 in, I think, 1,652 (sic) [1,675] people in France have the gene for porphyria. And one thing to realize is even if they're all latent, every single one of those is potentially a porphyria patient because all they need is one dose of sulfonamide antibiotics like I had and their porphyria is woken up.

Akin Akinc - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Hemophilia Program*

That's a great point, Mary. Thank you. We've got another question here and says, wouldn't givosiran reduce ALA/PBG at the expense of a patient's ability to produce hemoprotein? And if the heme synthesis pathway is already defective in AHP patients, would givosiran result in an even greater defect? And I'll maybe hand that over to Jae.

Jae Kim - *Alnylam Pharmaceuticals, Inc. - VP of Clinical Development*

Thanks, Akin. That's a terrific question. It's a question that we had really thought carefully about at the -- even before this investigational drug went into people. And so it turns out that the target for givosiran aminolevulinic acid synthase comes in 2 forms, ALAS1 and ALAS2. But it turns out that the form of this enzyme that is important for the generation of red blood cells is only expressed in red blood cell precursors. So givosiran targets the form called ALAS1, which is expressed in the liver. So givosiran's ability to knock down ALAS1 has absolutely no impact on the ability for red blood cell precursors to generate heme that goes into red blood cells. So it's quite elegant solution for that problem. Now you might ask what does heme do in the liver. And it has a relatively limited number of roles in the liver. So it does feed into some proteins that might metabolize drugs and chemicals called cytochrome P450, and these have been extensively evaluated in the -- in nonclinical studies and in clinical study. So overall, the impact is modest, and it's closely monitorable in our clinical studies. So thank you.

Akin Akinc - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Hemophilia Program*

Thanks, Jae. We've got another question here about ENVISION and enrollment and when we would have full attack data. I think as we've said before, we hope to complete enrollment in ENVISION late this year. And based on the 6 months double-blind period, we would expect to have full study data, including attack data importantly by the middle of next year, so mid-2019.

I think maybe we have time for one more question. And perhaps, I'll -- we should end with Mary. There's a question here for Mary. You mentioned that, Mary, a little bit about how the disease can be isolating. Can you talk a little bit about your family and your support network and your ability to connect with other patients with porphyria? When were you able to kind of develop those networks? Maybe talk a little bit about that.

Unidentified Participant

Yes. Thank God I have a very close family because while at 25, I bought my own home. At 50, I am living with my parents. I have been on disability for about 18 years now because of the debilitating back and leg pain and the paralysis in my hands and wrists. For people who don't have their family to rely on, I don't know what they would do just because I can't even count the times that my father has had to take me to ER or to -- admitting at the hospital at 1:00 in the morning. There is no way you could get there yourself. It would just be too hard, so I am grateful every single day for the family that I have and that they are here for me. The other part of support network would be things like the American Porphyria Foundation, which is a patient advocacy group. When the doctor in ER first thought of porphyria way back in 1995 or '96, almost pre-Internet, they somehow tracked down the home phone number of Desiree Lyon, the Executive Director of the Porphyria Foundation. And at 10:00 at night, she told them exactly what she wanted -- or what they needed to do and the 2 labs in the whole U.S. where you could send the lab samples to be tested and exactly what tests to order. So for the last 22 years, I've been a member of the American Porphyria Foundation. I've met some great friends through them. They've got a website. They've got Facebook pages. So just different forums that -- it's really nice that every day, you can go on. And no matter how sick you are, you can find people who understand. And that alone makes this less isolating. Seriously, Facebook is probably one of the best things that ever happened for porphyria. Because before that, most of us had never "met" anyone else with this disease because it's so rare. So the support they provide and just their links like working with Alnylam for the Alnylam Act and helping to find patients, they really have been a great support for so many of us patients.

Akin Akinc - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Hemophilia Program*

Thank you, Mary.

Unidentified Participant

Was there more to the question?

Akin Akinc - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Hemophilia Program*

I think we're just wrapping up now. I'm going to hand it over to Christine.

Christine Regan Lindenboom - *Alnylam Pharmaceuticals, Inc. - VP of IR & Communications*

Great. Thank you, Akin, and thank you to all of our speakers as well.

This concludes our RNAi Roundtable for today. The replay and the slides will be posted on the Capella section of the Alnylam website later today at alnylam.com/capella, with a transcript to follow shortly thereafter.

We hope you could join us for our next RNAi Roundtable on Wednesday, August 15 at 10:30 Eastern time as we discuss lumasiran and the development for the treatment of primary hyperoxaluria Type 1. For more details, please visit alnylam.com/capella.

Thanks, everybody. Have

(technical difficulty)