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ALNY - 2017 RNAi Roundtable: Givosiran, in development for the treatment of acute hepatic porphyrias

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Co. provided an update on givosiran investigational RNAi therapeutic program.

SEPTEMBER 07, 2017 / 2:30PM, ALNY - 2017 RNAi Roundtable: Givosiran, in development for the treatment of acute hepatic porphyrias

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Joshua Brodsky

CONFERENCE CALL PARTICIPANTS

Eliane Sardh

PRESENTATION

Operator

Thank you, ladies and gentlemen, for joining today's RNAi Roundtable. (Operator Instructions)

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

Joshua Brodsky

Good morning, everyone. Thanks for joining us for today's RNAi Roundtable to discuss givosiran, in development for the treatment of acute hepatic porphyrias. I'm Josh Brodsky, Associate Director of Investor Relations and Corporate Communications at Alnylam. With me today are Jeff Miller, General Manager of the givosiran program; Jae Kim, Vice President of Clinical Development; and Dr. Eliane Sardh of the Porphyria Center Sweden, Karolinska University Hospital.

Today's RNAi Roundtable is part of a series of roundtables that we have been hosting over the past several weeks. The event today is expected to end at around 11:45 AM. Jeff will moderate a Q&A session at the conclusion of the presentations. And if you'd like to submit a question, you can do so at any time during the event by clicking the Ask a Question button that is located above the slide window on the webcast player. Also, as we mentioned in our press release and subsequent conference call this morning, we will be postponing the fitusiran RNAi roundtable that was previously scheduled for September 12 to a later date.

Finally, as a reminder, we will be making forward-looking statements on today's webinar, and we encourage you to read on those recent SEC filings for a more complete discussion of risk factors.

And now with that, I will turn it over to Jeff.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Givosiran Program*

Thank you, Josh, and good morning, everyone. Welcome to our roundtable focusing on givosiran and the acute hepatic porphyrias. As many of you heard earlier, we believe we are now 1 step closer to hopefully bringing givosiran to patients suffering with acute hepatic porphyrias and are looking forward to sharing with you some of the details here today.

Next slide, please. As you know, here at Alnylam, we are driven to bring forward a new class of medicines and that is RNAi therapeutics. You can see here on the side some of the key elements where we harness the natural pathway or the catalytic mechanism. We're able to silence any gene in the genome, and we think there's an obvious benefit here as where targeting upstream of today's medicines. And when you look at the programs that we have today, we believe that this is a clinically proven approach.

And when you now turn to the next slide, what you see here is evidence of that. You see 8 clinical programs across 3 STARs and 4 late-stage programs. And focusing here on patisiran, fitusiran, inclisiran and givosiran, having 4 programs in late-stage development is truly an advancement in therapies for many patients suffering with these diseases as you see here.

Turning to the next slide, and as you know, today's roundtable is going to focus on givosiran. And givosiran is being studied for the acute hepatic porphyrias, which you know was also very, very exciting as now we're turning very quickly from our Phase I program to the Phase III program. And beyond that, givosiran is our first program that we own commercial rights globally. So we look forward to developing givosiran and then hopefully commercializing this drug to patients around the world who are suffering with the acute hepatic porphyrias.

Next slide. At this point in time, I'd like to welcome Dr. Sardh. Dr. Sardh is from the Porphyria Center Sweden at the Karolinska University Hospital. Dr. Sardh is a world leader on porphyria and is extremely well published in this space. Dr. Sardh is going to provide an overview of the disease, the acute hepatic porphyrias. We'll walk through some of the key aspects of the EXPLORE Natural History Study, the first of its kind in the acute hepatic porphyrias. And then we'll spend some time reviewing the Phase I clinical data for givosiran.

With that, I'll turn it over to you, Dr. Sardh. Welcome, and thank you for joining us.

Eliane Sardh

Thank you, and good morning, everyone, from Sweden. And can I have my first slide, please?

Heme biosynthesis takes place in all nucleated cells in the body. Approximately 80% is produced in the bone marrow and is used for oxygen transport in hemoglobin. The rest is mainly produced by the liver and used for different and somatic processes like detoxification of toxins and pharmaceuticals as well as being involved in many regulating processes in our metabolism.

There are 8 steps in heme biosynthesis, each characterized catalyzed by a specific enzyme. The first enzyme, aminolevulinic acid synthase is rate-limiting, and there are 2 tissue-specific enzymes completely different -- differently regulated: one in the bone marrow called ALS2, and one in the liver called ALS1. All of these enzymes, except ALS1, can -- due to gene mutation, have a reduced catalytic capacity, and hence, they are 8 different porphyrias as you can see on this slide.

The focus on this talk is the acute hepatic porphyrias, marked here by an orange color, and we will not discuss the other porphyrias, which are mainly erythropoietic that is affecting the bone marrow. Hepatic ALS1 can be mostly induced when the demand for heme increases in the liver, and this caused accumulation of porphyrin precursors, ALA and PBG as well as porphyrin before the deficient enzymatic step. These metabolites are toxic mainly to the nervous system and caused a dramatic event called the acute porphyria attack.

On the right-hand side of the slide, you see the different clinical manifestations associated with the different acute hepatic porphyrias where hereditary coproporphyria and variegate porphyria, besides the acute attack, also can cause skin manifestations such as scars and blisters.

Next slide, please. Even today in modern medicine, it is very difficult for patients to come to diagnosis, which is illustrated by this recent case of mine. This woman came to the ER with severe abdominal pain, but otherwise, very few clinical signs besides high blood pressure and mild hyponatremia, and she was therefore sent home. Due to rapid deterioration, she seeks again and again. And finally, after 78 days when she is completely paralyzed and in very severe pain, the diagnosis is made by an endocrinologist who used the combination of a young woman, severe abdominal pain and hyponatremia and then considered porphyria.

She has then had numerous examinations and had been evaluated by a number of specialists without conclusive diagnosis. However, as soon as you consider porphyria, the diagnosis is quite simple to make. From spot urine samples sent to specialist labs, and the diagnosis can then be confirmed by a mutation analysis.

Can I have the next slide, please? As mentioned before, the symptoms during the acute porphyric attack comes from all parts of the nervous system. The cardinal symptom is pain and often tachycardia and hypertension is present. Those patients have muscle weakness due to acute peripheral

neuropathy and common CNS manifestations or anxiety and insomnia as well as confusion. In the very severe acute attack, you can have acute encephalopathy and associated to that, very severe seizures. There are few metabolic manifestations like hyponatremia and mild liver function test elevation. And these, of course, make the diagnosis very difficult.

Can I have the next slide, please? Treatment is based on, if possible, eliminate any known triggering factor, treat the different symptoms symptomatically. And often, very high doses of morphine is required to ameliorate pain. Carbohydrate loading is often used and can ameliorate very mild attack. But the only specific treatment available today is human hemin, which then regulates ALS1 through feedback inhibition.

Can I have the next slide, please? Coming back to my patient who, after this very first severe acute attack, initially had to spend several months in a wheelchair. And when she had recovered, sadly moved into the approximately 5% group of the most severely afflicted acute hepatic porphyria patient, those suffering from recurrent acute attacks. In between attacks, she has developed chronic manifestations like chronic pain. She's very -- she has fatigue, nausea and insomnia. And the quality of life is extremely impaired. Sadly, she has had to give up a career as a professional ballet dancer.

Can I have the next slide, please? There are not many treatment options we have for this patient group. If female and the attacks on menstruation associated, you can chemically stop the ovulation cycle and make the female menopausal. Benefits must be carefully weighed, and the treatment can only go on for less than 2 years due to the side effect of estrogen deprivation, such as loss of bone density. Many of us used prophylactic hemin to avoid severe, long-lasting attacks. This is not an approved treatment, but it can ameliorate and increase quality of life for the patient. Although life-saving, there are a number of long term as well as short-term side effects associated to human hemin, and the treatment cannot go on for long due to this. And eventually, the patient will be presented to the transplantation team. Loss of venous access have to be carefully monitored since it can prevent the patient from the last resort we have, which is liver transplantation.

Can I have the next slide, please? The acute hepatic porphyrias are also associated with late complications like chronic kidney disease, hypertension, chronic pain and progressive neuropathy. Primary liver cancers are quite common, and you have an extreme -- extremely impaired quality of life. There is no specific treatment, only symptomatic or preventive, such as screening yearly for early detection of liver cancer. The pathophysiology of these complications is completely unknown, but the hypothesis is that they are caused by the permanently elevated porphyrin precursors, mainly ALA.

Can I have the next slide, please? For us working in the field, there are several unmet needs and areas for improvement in this field of acute hepatic porphyrias. We still have very limited knowledge of the pathophysiology of the disorder as well as the natural history. And international collaborations are needed to answer this question. We need better biomarkers for the disease since ALA and PBG probably are just surrogate markers, and the specific levels of porphyrin precursors do not correlate to the disease severity nor the risk for the patient to become recurrent. We are actually in desperate need for new treatment option since human hemin, although having saved many lives, is not an option for the treatment of the recurrent acute patient nor can it prevent the long-term complications to appear.

Can I have the next slide, please? I will now present some key data from the EXPLORE study, which is one of the international collaborations initiated by Alnylam to try to answer the question of natural history in the acute hepatic porphyria.

Next slide, please? In total, 112 recurrent patients with acute hepatic porphyria have been included in this observational study. The clear majority of patients having acute intermittent porphyria and only few variegate porphyria and hereditary coproporphyria. Also, as you can see, the vast majority of patients are women, approximately 89% are female.

On the right-hand side of the slide, you see the most common associated disorders with acute hepatic porphyria, which are renal and vascular disorders like hypertension, chronic kidney disease, nervous system disorders, headaches, neuropathy, psychiatric disorders like depression, insomnia and anxiety.

Next slide, please? On this slide, we show the number of attacks 96 of the observed patients experienced. It ranges from 1 to 37, with an overall yearly attack rate of 4.9. The mean duration of an acute attack is 7 days. When looking at subgroups, like patients having chronic symptoms compared

to no chronic symptoms, there is only minor differences in the yearly attack rate. If you look at the groups treated on hemin prophylaxis, there is a lower attack rate compared to those who are not, but they are not attack-free, which is actually the aim of prophylactic hemin treatment.

Can I have the next slide, please? Most patients are treated at hospitals during their acute attacks, but approximately 1/3 have their treatment as part of home care. There are countries in Europe, like the U.K., and also certain centers in the U.S., who have very well-organized home care teams for their recurrent acute attack patient so that they do not have to come to hospital when having an acute attack.

Next slide, please? Patients suffering from recurring acute attacks have very poor quality of life, as demonstrated on this slide. In red brackets are the numbers of those reporting moderate or severe problems. And you can see that 43% report moderate or even extreme pain of some sort; 28% having anxiety or depression; and 30% report moderate or severe problems in their usual daily activities.

Next slide, please? Here, we have the patient reported chronic symptoms they have, and you see that 65% of patients do report chronic symptoms, most commonly pain, tiredness, anxiety and nausea; and as many as 46% of them report having daily symptoms.

Next slide, please? In the coming slides, I will present some interim data from the Part C part of the Phase I study of givosiran as well as the interim data from the open-label extension study of the trial.

Next slide, please. As we've said, the pharmaceutical mechanism for givosiran is based on RNA interference, which is the natural pathway in cells. Synthetic double-stranded silencing RNA is targeted to the liver by the ligand N-Acetylgalactosamine, GalNAc, which has a very high affinity for the asialoglycoprotein receptor on the hepatocyte. Once in the hepatocyte, it mediates ALS1 down regulation, leading to a reduced production of heme precursors, ALA and PBG, which are associated with symptoms during the acute attack.

Next slide, please? This is an overview of the study design and objective for Part C and open-label extension study. Part C is a double-blind, placebo-controlled study, and the key inclusion criteria are genetic confirmation -- confirmed diagnosis and the patients have had to have at least 2 acute attacks in the past 6 months, and if they were on prophylactic treatment, be willing to stop. The objectives are primarily safety and tolerability as well as PK and PD data, but also clinic activity on attack frequency and treatment is monitored.

As you can see, the study started with a 3-month run-in period, where patients' attack frequency and treatment was monitored as well as quality of life data. During this run-in period, at least 1 attack was necessary for randomizations. Patients were then randomized into 4 different cohorts: Cohort 1, dosed at 2.5 milligram per kilogram quarterly; Cohort 2, 2.5 milligram per kilogram, monthly; Cohort 3, 5 milligram per kilogram dosed monthly; and the last cohort, 5 milligram per kilogram dosed quarterly.

After the 6 months treatment period, patients were randomized into the open-label study, which has 4 cohorts as well as you can see on the slide. Please note that the first cohort in the open-label extension has twice the dose of the corresponding cohort in Part C.

The results that we present come from the first 3 cohorts of Part C, and interim data from the open-label come from the first 2 cohorts.

Next slide, please. The disease severity by cohort is demonstrated on this slide, and you can see that the severest patients are in the first cohort, with a mean annualized attack rate of just over 38. In the second cohort, the mean attack rate was almost 17, and in the third cohort, approximately 13. In the first Cohort, 3 patients had, before run-in prophylactic heme treatment, 2 patients in Cohort 2 and no patient in Cohort 3. The levels of ALA and PBG were quite similar in all 3 Cohorts.

Can I have the next slide, please? On this slide, you see the effect of givosiran on urinary levels of ALA and PBG, expressed as percentage of change from the run-in period to the treatment period. In Cohort 1, the change was approximately 42% for ALA, and 30% for PBG. In Cohort 2 and 3, the percentage of change was approximately 75% for both ALA and PBG. The differences between cohorts may be that the levels of ALA and PBG were much more variable in Cohort 1 than in Cohort 2 and 3, probably due to the lower dose in Cohort 1, allowing induction of ALS1 in between doses.

Next slide, please. On this slide, we demonstrate the clinical efficacy of givosiran as decreased annualized attack rate in Cohort 1 to 3. On the left side of the slide, you have the decrease in each cohort compared to the 3 placebo patients, and the mean for all 3 cohorts was a 63% reduction.

On the right-hand side, we show the reduction in annualized attack rate in the placebo-adjusted calculation for the different 3 cohorts. As a mean, we see for Cohort 1 to 3 a 73% treatment effect compared to placebo.

Next slide, please? Another way of demonstrating treatment efficacy is by decreased annualized hemin doses. The decrease was prominent in all 3 cohorts, with a mean of 73%.

Next slide, please? On this slide, we demonstrate the efficacy of givosiran to reduce annualized attack rate by percentage of lowering of ALA. The lowering is presented in quartiles from patient's baseline. And you can see that by lowering ALA more than 75% from patient baselines, you have the best effect in attack rate reduction.

Next slide, please. These are the same efficacy shown back for PBG. And also here, you can see, by reducing PBG more than 75% from patient baseline, you have the best effect in reduction in yearly attack rate.

Next slide, please? Here, we have also included efficacy data from the first 2 cohorts of open-label extension study for comparison. Also, the open-label study demonstrates the maintained and even enhanced treatment effects compared to Part C regarding annualized attack rate, as you can see on the left side, as well as reduction in hemin doses, demonstrated on the right-hand side on the slide. You have to remember also that the patients in Cohort 1 of Part C received 2.5 mg per kg Q3; and in open label, the dose is twice as high as they are having 5 mg per kg dose quarterly.

Next slide, please? Here is very exciting data. From the first 2 placebo patients in Part C who, who, when moving into open-label extension study, has not have -- had any acute attacks since being dosed. Both patients come from my side at Karolinska University Hospital, and actually, none of them have had any acute attacks since being dosed, which is now approximately 5 months ago.

Next slide, please. So in summary, we can conclude that givosiran has been demonstrated to be both safe and tolerable, and there has been no discontinuations due to adverse events or other clinically significant changes in EKG, vital signs or laboratory reports. In Part C, we had 4 serious adverse events, including 1 fatal, which has been discussed before. But none of them have been assessed to be related to the studied drug. 4 patients has had -- have had drug-related adverse events like injection site reactions, which have been both mild and self-limiting. Safety and tolerability are consistent with Phase I for open-label so far and no serious adverse events for discontinuation due to adverse events have taken place.

And with this slide, I thank you for your attention.

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

Thank you, Dr. Sardh. This is Jae Kim, Vice President, Clinical Development at Alnylam. And I'm pleased to provide an update on givosiran's regulatory status and an overview of the planned Phase III clinical study.

Next slide, please. We're on Slide 37. As Dr. Sardh has shown, givosiran, a 1-monthly subcutaneous drug, has the potential to be a transformative therapy for acute hepatic porphyrias. There has been substantial progress in the regulatory authority front and our interactions to date. The disease epidemiology, seriousness, unmet medical need and potential for significant benefit over existing therapy has resulted an orphan designation by both the EMA and the FDA. In addition, the potential substantial improvement in care of these patients with very high unmet need and the incredible promising early clinical evidence in givosiran's Phase I clinical trial data has resulted in acceptance of givosiran as a priority medicine, or PRIME, scheme with the EMA, and breakthrough designation with the FDA. Our interactions thus far has led to alignment on the overall Phase III study design with the EMA and the FDA. And I'm very happy to announce that the Phase III study has gained additional alignment with the FDA, with a reduction in urinary ALA levels at 3 months of treatment as a biomarker that is reasonably likely to predict clinical benefit, an aspect that I'll expand on the subsequent slides.

Next slide, please. Alignment with the FDA on the interim analysis provides an opportunity for accelerated approval based upon a biomarker endpoint of ALA levels. And the 4 Phase III clinical study results at the end of the Phase III period can provide robust confirmatory data. On the left panel, we show givosiran targets the liver-expressed ALAS1 MRNA, which is the enzyme upstream of the genetic defect on acute hepatic porphyrias.

When moved to the middle panel, it will show that ALAS1 is responsible for overproduction of ALA, a causal toxic in synthesis intermediate responsible for porphyria attack. The lower-middle panel shows our own Phase I data with single doses that shows ALA levels are efficaciously and durably reduced by givosiran and can be the basis for the initial U.S. approval. I draw your attention to the x-axis here on this plot. These numbers are months after single doses, not weeks or days.

Then on the right-hand panel, after the use of ALA as a surrogate biomarker, on the right, we show that the full Phase III results can provide confirmatory data with 10 points of directly measured clinical benefit, such as reduction in porphyria attack, reduction in intravenous hemin doses and improvement in symptoms and quality of life.

Next slide, please. Here, we show that lowering ALA is reasonably likely to predict clinical benefit in porphyria patients. ALA is late in the biological pathway. That is to say that ALA itself is a causal factor of disease manifestation. And lowering of ALA with other interventions, for example, hemin, liver transplant and other interventions, has been shown to predict reduction in porphyria attack. Here, we have more pivotal evidence outside of givosiran to show that reduction in ALA can have meaningful impact in clinical events.

And finally, there is a continuous relationship between ALA lowering and attack reduction. On the left panel, natural history data shows clear relationship between ALA levels and porphyria disease activity. You see here populations of acute attack patients, those patients with -- who are symptomatic but in remission; those who are asymptomatic and healthy relative; and you can see a continuous relationship of ALA levels and degree of clinical activity.

On the right panel, we show interventional data in our own givosiran Phase I clinical trial. That reduction in ALA is correlated with reduction in porphyria attacks. So in the combination is not only observed data in populations, but also in the interventional study with givosiran, we show a powerful correlation between ALA and disease activity, and that lowering ALA can improve or reduce disease -- attacks that are severe in nature.

Next slide, please. Interim Phase I data from -- with givosiran has the 2.5 milligram per kilogram per month dose level. The take 4 measurement in the Phase III registration study achieved large and pumped reductions in ALA. From highly elevated in the current attack patients as shown here, with patient baseline ranging from 14 to 20 millimoles per mole Creatinine. They're within the normal range with givosiran treatment. What is striking is that with the upper range of normal ALA at 3.8, givosiran achieved an ALA level of 1.5 with an incredibly tight standard deviation.

Next slide, please. On Slide 41. Here, we summarize the givosiran Phase III study design. With a plan to initiate the study by late this year, the study has a randomized, double-blind, placebo-controlled study, followed by an open-label extension of up to 30 months of treatment. We plan to enroll approximate 74 patients with acute hepatic porphyrias, aged 12 and older, with clinically active disease defined as having 2 or more attacks within the prior 6 months. Givosiran -- the patients are randomized one-to-one to subcutaneous givosiran monthly or wind up with placebo.

The composite primary endpoint is annualized rate of porphyria attacks requiring hospitalization, urgent care visits, home IV hemin. And this composite endpoint is an objectively measured and a hard endpoint that encompasses greater than 70% of all attacks in this population. Key secondary endpoints include ALA and PBG levels, hemin doses, symptoms and health-related quality of life. The current design is adequately powered for the primary endpoint of attack as well as for the interim analysis. There's no plan to stop the study early for efficacy or futility, and we -- and at the end of the trial, we'll provide fully mature data on the clinical impact of givosiran in acute hepatic porphyria.

The Phase III study will have a global footprint across 22 countries, including North America, Europe, Asia and South Africa. Of note, the interim analysis will be performed when 30 patients complete 3 months of treatment, yielding a mid -- approximate mid-2018 interim readout, supporting a potential NDA at or around year-end of 2018 as positive, with a potential FDA approval early to mid-2019.

We hope that this will be a fantastic study. Thank you.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Givosiran Program*

Thanks, Jae. So that is certainly exciting news indeed, and thank you to Dr. Sardh for taking us through an extensive but very quick look at the natural history of the disease and then also the clinical data for givosiran.

What I'd like to do now is talk a bit about program time lines, touch on strategy. Certainly, with the time left here at this roundtable, we'll only touch on some of the key elements at a high level. But the idea is to begin to give you a feel for how the organization is thinking about bringing this medication to patients as quickly as possible.

Next slide, please. So laying this all out in a very simple way, here are our assumptions moving forward. We intend to start the Phase III later on this year. As Jae mentioned, the interim analysis is targeted for the middle of next year, at or around the end of next year. With positive data, we hope to file givosiran in the U.S., which puts us looking at a U.S. approval in the early to middle part of 2019.

Next slide, please. So within the framework of those assumptions, it's important to step back and say, well, we are at this juncture, less than 2 years from potentially commercializing givosiran and bringing it to patients in need here in the U.S. And that presents an immense amount of opportunity and work to be done.

So let's focus on 4 key elements here over the next couple of minutes. We'll lay them out in this way. The first part is in the upper left corner, and what we're calling map the patient journey, and there's a couple of subitems there. First and foremost, further clarifying the epidemiology. I'll touch on this more in just a moment on a subsequent slide. As it relates to the porphyria physician network, there is an incredible network in the U.S., the American Porphyria Consortium, who's done a lot to advance the work of treating these patients in the U.S. The EPNET, the European Porphyria Network, in Europe as well has done an immense amount of work, and we intend to work very closely with them to help bring givosiran to patients quickly.

One of the key steps in really understanding this market is understanding where patients are being treated today. Some of the work we have done suggests that there are a fair number of patients who are undiagnosed but being treated by some specialties, which, again, I'll get into in a minute. And we want to make sure we can clearly understand where those patients are and what the referral networks are so that we can help encourage them to get to the right specialist, ultimately get diagnosed and to be treated.

Moving to the upper right corner in the red box, as you can imagine, a key element here is to focus on partnering with the patient advocacy groups. The American Porphyria Foundation has done an immense amount of work as well to help create awareness of porphyria in the United States, and we intend to work very closely with that group moving forward as well. One key part of education, of course, in many rare diseases is to better define the disease and what are called the red flag symptoms. And you've heard Dr. Sardh and Jae go through what are some of the hallmark symptoms of porphyria. We need to help educate the physician community and the patient community as well on what those hallmark symptoms are, those red flag symptoms are on the journey to helping to improve diagnosis and to shorten that patient journey. We've heard and seen numbers as high as 15 years' time to diagnosis, which is incredible when you think about the pain that many of these patients are in, the repeated attacks and the chronic symptoms. So the goal really here is to help improve education with the patient advocacy groups, with the physician groups, and help shorten the journey and improve the rate of diagnosis.

Moving to the lower left corner, of course, a key element of success here is ensuring rapid access, and of which, we work very closely with the payer and the provider networks around the world to help them understand what the economic burden of porphyria looks like. There were some data published back in June, which I'm going to show you in just a few moments, that is a stark, clear reminder of what this disease costs that not many people knew. And I think that's an important thing to take in the context here is within this final bullet, characterizing disease chronicity, there may have been a perception historically that this was a disease where patients have attacks and then they get better. It certainly seems that, yes, there is a time of an attack, but also, many, many patients are reporting chronic symptoms. As you saw on one of the slides that Dr. Sardh presented, up to 2/3 of patients report chronic symptoms and nearly 1/2 of patients report daily symptoms. That's quite different than, perhaps, other disease was viewed historically. And that's something we want to help payers understand as well.

And finally, launch readiness and expansion. One of the benefits that givosiran has is that we'll be launching after fitusiran, and that's a benefit to patients and physicians, we believe, because we'll have an already built infrastructure, both in U.S. as well as in Europe, that we can leverage to help get the product to the physicians, to the patients as quickly as possible. It'll also help us be able to rapidly staff up upon gaining the approvals. And then very exciting, of course, is rest of world. The epidemiology, with the exception of a few countries, doesn't suggest there are different rates of porphyria, with the exception perhaps of the Nordics and Sweden, Dr. Sardh can comment on this as well, and in South Africa. But the rate of porphyria appears to be common around the world, and we're very pleased to have this as a global program. And we're very excited to work through the different commercialization options to help bring givosiran to these patients around the world. That's a few years down the road, of course, but that is also in process. And then finally expanding patient eligibility. A lot of work right now is going into, what else can be done with givosiran? There are, as you heard Dr. Sardh referenced, some secondary complications of elevated -- chronically elevated ALA and PBG. There may be some opportunities there as well. But again, that's a discussion for a different day, but these are the key elements to focus in on today.

Next slide, please. So as it relates to epidemiology, as with many rare diseases, the epidemiology is not well understood. There are some papers out there right now, and you see the consensus estimates there as well as the ratio of AIP to VP to HCP. Using those numbers, what we believe right now, today, is that there are between 1,000 and 1,500 patients with recurrent AHP around the world. And again, with the ongoing work that we're doing, we believe that number could likely be higher through some of the research that's going on right now. Database analyses and discussions with key opinion leaders as well as others in the field suggest that there are a fair number of patients today who are misdiagnosed and are being treated by -- being treated for something else other than porphyria. And that's, again, an opportunity for education. When you think about the symptoms of this disease, it's very, very difficult to diagnose because it can be intermittent at times. So that's an area of improvement. But we think for today, landing in this spot in terms of the epidemiology, certainly suggests that there are sufficient number of patients out there today suffering that givosiran we hope can help.

Next slide, please. Now looking at the management of porphyria. A couple of things to sum up a very complex slide. It's complex because the patient journey is complex. There's a long journey, many, many specialties involved. What we've found is that the options to test are not well understood, and in some places, not available. So there's a lot of work to be done. But starting here on the left, what we find in the journey is that these patients quite often present to the emergency room first, and sometimes, many times over, thinking about Dr. Sardh's case, patient being in and out of the hospital for 78 days. You look at also the EXPLORE data, the average -- the mean number of attacks per year was 5, and the duration of the attack was 7 days. So very simple math tells us, that's about 1 month in the hospital per year when you figure that about 2/3 of attacks require hospitalization. That's a very, very difficult disease, and it's something that we're starting to learn more and more about.

So as we you through the cycle here, the frontline and then the escalation, other specialties are brought on board. Eventually, at some point in time, and this does take some time, there's a suspicion of porphyria. The patients often play a role. They're very active. They search for information. And when the time comes to get the proper diagnostic workup, the diagnosis can be made, and then the patient can be managed. Now the challenge there -- and this is a generalization, and it's important to note that this research here that I'm commenting on is from the U.S. only. This work is going on in Europe right now. There are some outstanding centers of excellence here in the U.S. as well as in Europe, but there are few. I think there are just a handful. Moreover, the knowledge of those centers of excellence within the U.S. is still fairly low. So again, there's an opportunity to help build those networks, to help put doctors into contact with the specialists. And one of the things that we're finding is that for patients who may actually be treated, a lot of them are being treated locally, not by a porphyria specialist. So huge opportunity to help educate, huge opportunity to help bring patients closer to a diagnosis, hopefully on a much shorter period of time.

Next slide, please. Now turning to the second aspect of education, and again, this is U.S.-based research. Starting with some of the physician specialties who touched the patients with porphyria. And you see here hematologists, gastroenterologists, neurologists, emergency room, internal medicine and then the OB-GYN. And you can see how their current knowledge is best described in the bottom of the slide, and this is self-reported. So again, when you think about the patient case being put in front of these physicians, the porphyria patient -- porphyria, as a disease group, is not at the front of their mind. It's something that, certainly, when presented and more information is shared, the diagnosis can be made. But today's state of education -- state of knowledge, rather, is low, and therefore, the opportunity to educate is quite high. And of course, that's going to vary by specialty. But you see here, just by looking at this alone, the magnitude of education required, but then also the number of specialties that will need to be addressed to improve the awareness of porphyria.

Next slide, please. This is a patient point of view as it relates to porphyria. This has been often described as debilitating, certainly unpredictable and life-altering. Dr. Sardh's case certainly spoke to that. You see here that this classic presentation of the abdominal or chest pain with the nausea is the -- is what prompts the search for diagnosis. But then, what we found is the number of diseases a patient might be misdiagnosed with is rather extensive. I won't go into all of them here, but you can see that there's a long list. Often, patients are thought to have psychiatric disorders because the awareness of porphyria is low. And sometimes labeled as drug-seekers because the pain is so high. Again, one of the challenges here, because the disease progression not being linear, and you can see the illustration at the bottom, and this isn't intended to be specific to 1 particular patient, but rather a blending of different cases that we've seen. The frequent hospitalizations is really the challenge here, which is where our Phase III will be measuring reduction in attacks that require hospitalization. So a very clear correlation to the unmet needs in the marketplace today and what we intend to evaluate in our Phase III program.

Next slide, please. Now turning to the economic burden of AHP. This is something that was presented at the ICPP Congress back in June. And a pause here, just to reflect on the numbers. The cost of this disease is substantial, and to the best of our knowledge, this is the first time an evaluation of this kind has been done. And what you see here is that the annual expenditure per patient per year that is diagnosed with porphyria ranges from $400,000 to $650,000. You can see the split here of the costs between hospitalizations, the heme costs and some of the others. And of course, depending upon what assumption you use, and those are outlined on the box -- in the box at the bottom, you'll get a different number. But keep in mind, these are patients who are diagnosed with porphyria. You can imagine patients who are out there today who are going to the emergency room every 6, 8 weeks, 12 weeks, seeing their primary care physician, their internal medicine, different specialists and not being diagnosed, and what types of costs this puts on in addition to the patient burden. This is an extensive, expensive burden on the health care system. And that is our intent to work with payers to help them better understand their patient population and what the cost of this disease means to them and what we hope that givosiran will help to relieve in the future.

Next slide, please. And with that, now let's turn to the time lines and how we're thinking about sequencing launches. So first and foremost, as stated earlier, assuming positive results, we are planning for a U.S. approval in mid-2019; Europe, in the late '19 or in the early to mid-part of 2020. Japan would come 6 to 12 months after that. And as I touched on earlier, right now, we're going through a deep evaluation process of how to best commercialize givosiran, how to best bring this drug to patients around the world. Keeping in mind that we also have another global asset here at Alnylam which is ALN-CC5, so that's also an opportunity for the organization to begin to think about expansion beyond the U.S. and beyond Europe, and really puts us in a position to bring 2 innovative therapies forward to patients around the world.

Next slide. So with that, let us turn to Q&A. Josh, what do you have in terms of questions coming in?

QUESTIONS AND ANSWERS

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Givosiran Program*

Okay. The first question is -- okay. Dr. Sardh, maybe you could handle this one. The first question that's coming here is around the -- how many patients or percent of patients would you say here have chronic pain, touching on some of the things we talked about earlier regarding chronic symptoms? And what are your thoughts on givosiran's ability to help there? And then Jae, of course, I invite you to comment as well. Dr. Sardh?

Eliane Sardh

Yes, thank you. And as Jeff has said, we are not so knowledgeable about the natural history of acute hepatic porphyrias. But as shown from the EXPLORE study, approximately 2/3 of the patients do report chronic symptoms. We think that those chronic symptoms are associated to high levels of ALA and PBG and also having repeated attacks, which is very deleterious for the nervous system. And hypothetically, it could be treated by giving givosiran, but this has to be further explored later on, I think, before administering givosiran to all patients having also chronic pain.

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

Thank you, Dr. Sardh. This is Jae Kim. Yes, as Dr. Sardh has mentioned in our EXPLORE Natural History Study, approximately 2/3 of the patients suffered from chronic symptoms, most of which -- most commonly, pain, so along with tiredness and nausea and anxiety. So this is a symptom that we'll be evaluating in Phase III and that we hope that we'll be able to provide some definitive data on that one.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Givosiran Program*

Great. Thank you, Dr. Sardh. Thanks, Jae. So the next question here, given the announcement about ALA reduction being an acceptable endpoint for the FDA interim, the interim approval, how does that square with the primary endpoint being the attack rate? And then have we given any consideration to resizing the study? But Jae, maybe you could comment on the relationship here between ALA at the interim and then attacks for the full data set?

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

That's a great question, Jeff. So the -- it is a great win for our program that the FDA acknowledges that ALA, as a causal factor of disease, can be considered as a surrogate endpoint. And what I mean by surrogate is that it is a biomarker measurement that is thought to be reasonably likely to predict clinical benefit. And the -- a clinical benefit is really how people feel, function and survive. So ALA in itself is a measurement of something that we measure the urine, and the feel, function, survive are the endpoints -- the clinical endpoints that are represented in the Phase III study. Now what it really comes down to as it relates to the FDA has -- is making that leap in the strong correlation of ALA with clinical outcomes. So this is kind of a stage thing. So I'll give you an example is that LDL cholesterol is thought to be responsible for heart attacks. So the FDA can provide an approval based on LDL cholesterol lowering, and that a follow-up study can be done to show that LDL cholesterol lowering by a given drug can result in reduction in heart attacks. In our case, as the FDA has acknowledged to allow us an initial approval based on ALA lowering, provided that we meet that endpoint. Now the confirmatory data will show that ALA lowering by our drug leads to an improvement in how patients feel, function and survive. So our primary endpoint is a composite of the severe attacks that is defined as attacks leading to hospitalization, urgent care visits or intravenous hemin administration. But these are the bulk of the attacks in this -- in the population that we're studying. So the other question with regard to sample sizing and, I assume, power, is that at the interim also, we will be evaluating attack rates and utilizing an independent data monitoring committee, and they will have the ability to adjust sample size based on the attack rates observed in the study. So please be reassured that our using that mechanism is not in any way related to any decreased enthusiasm of our being able to hit attack reduction. It is a reality in human clinical study that we need to be able to design the study so we can win. We know that we have a very potent drug, and so we are providing the study an opportunity to win irrespective of the attack rates that are observed coming into the trial.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Givosiran Program*

Great. Jae, thanks for talking everyone through that. So keeping with the theme of ALA, a question here around the ALA biomarker diagnostics. So is the biomarker currently commercially available?

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

Yes. So the biomarker is used clinically, and I'll take a first stab at this question, and I'm hopeful Dr. Sardh can provide further granularity. But the delta aminolevulinic acid can be performed as a plasma or a urinary study. It is not widely available, and that there are clinical labs that samples can be shipped to, to provide the results in a couple days. But Dr. Sardh, can you expand on that answer a little bit?

Eliane Sardh

Yes, I can explain from the European and Swedish perspective. Since this is -- ALA is analyzed at highly specialized laboratories, and you do need to have a very good quality at the laboratory to have certain -- to be sure what you are actually measuring. On the other hand, ALA and also PBG

are very closely associated to the conditions. So if you have elevated ALA, you do have a very strong suspicion of porphyria patient. Is that answering your question? Or was the question regarding how many labs you have that are analyzing ALA? Or what was -- did I understand the question correctly?

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Givosiran Program*

Yes, Eliane, it was well understood. I think the question here gets to, is there an intent here to make it a companion diagnostic? And the answer is no. However, what the question highlights is that, even in the U.S., there is a need for a rapid diagnostic and what we have patients -- what we have is patients, of course, entering to the emergency room, and that is an opportunity to help improve diagnosis in absence of a rapid diagnostic that is widely available, that slows down the diagnostic process. It slows down -- it increases, rather, the time to -- it increases the patient journey, and that's something that we're looking at as an option to address.

Eliane Sardh

Yes, I can also -- sorry, that there are places in, let's say, Eastern Europe who do not have access at all to porphyria specialist labs. So there's a lot of things to do around making it available for -- even for countries to have this analysis at 1 specific laboratory, which is not the case in many countries, actually.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Givosiran Program*

Good. Thank you, Dr. Sardh. So the next question we have here -- Dr. Sardh, I'll turn this question to you. You touched on it in your -- in one of your slides. And the question is, how common is liver cancer? So getting to some of the complications of chronic elevations of ALA and PBG, how common is liver cancer? And what appears to cause it? Do we know?

Eliane Sardh

Regarding how common it is, it's -- we -- actually, it has not been studied very closely since the sort of mid-2000s. There has been case reports since the beginning of the '80s that patients having acute hepatic porphyrias have a higher frequency of primary liver cancer. In Sweden, we did a survey of our patients, and we found that approximately -- the risk is approximately 60% higher if you have a mutation in one of the acute hepatic porphyria genes compared to healthy, controlled population, age match and so on. In the rest of the world, it has not been systematically investigated. So we are actually in the beginning of this field to say how common it is. For instance, in the U.S., we don't know. But in Sweden, the studies we have performed has led to a national survey program where all patients over the age of 50, every year, should have an ultrasound examination of the liver for early detection of primary liver cancer. And in my center, we find approximately 1 cancer patient each year. The question is whether it's associated to chronic -- to active disease, whether patients who have had many acute attacks are at a higher risk than those who are only latent gene carriers. This question is unknown. And this also relates to the past physiology of primary liver cancer and the acute hepatic porphyrias. We do not know. What we know is that it somehow points to ALA since patients having tires tyrosinemia type 1, which is another inborn error of metabolism. Those children have very high levels of ALA due to inborn errors in the amino acid tyrosine metabolism. And they have a very high frequency of primary liver cancer even in childhood. So we do think ALA is implicated in some way. But on the other hand, we also have patients who have never had any acute attacks and do not have chronic elevated ALA and PBG who do have -- also are diagnosed with primary liver cancer. So this is a field we have to research much more into, but there is a clearly higher risk having acute hepatic porphyria to have primary liver cancer. That is for sure.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP and General Manager of Givosiran Program*

Excellent. Thank you so much, Dr. Sardh. One final question here, and then we'll summarize and wrap up. So the question comes in around what is the status of the discussions with other regulatory authorities, specifically Europe? So as mentioned before, as this is a global program, we are engaging with the regulatory authorities in Europe, in other countries as well. At this juncture, it's premature to comment on how that will go.

However, we believe that with givosiran being awarded PRIME in Europe, that's a very positive sign. The regulators have been incredibly supportive of the program so far. They see the unmet need, and we're actively in dialogue with them. So as -- certainly, as more information becomes available as it relates to Europe specifically, and I won't venture further beyond Europe at this juncture, we'll be happy to share that with you. So certainly, not enough time to answer all of the questions that have come in, but let's take a minute to pause and summarize what we heard today.

So the acute hepatic porphyria is a group of ultra-rare orphan diseases with devastating manifestations and high unmet needs. The work that has been done to understand porphyria over the years has been outstanding. We are certainly privileged to be a part of that now and really helping the educational effort move forward to better characterize this devastating diseases.

The EXPLORE Natural History, I think, shows a couple very key things. When these patients have attacks, more often than not, they wind up in a hospital or in the emergency room, putting immense burden on the patients and also on the health care system. They suffer from a dramatically reduced quality of life with chronic symptoms for many, many patients.

That targeting ALAS1 upstream of the genetic defects, we think, is the right target. The clinical evidence supports that. The Phase I data, the OLE data, very, very powerful. What Dr. Sardh pointed to, those 2 patients who were highly active in terms of number of attacks during the double-blind part of the study who were on placebo have now been on givosiran and the OLE, and have no attacks for up to 5 months. That speaks to -- we believe, speaks to the power of the drug to lower and clamp ALA and PBG, which correlates with the clinically efficacy.

Very, very positive news. We hope everyone's sharing in this happiness with us that we've aligned with the FDA, we've aligned with EMA on the design of the Phase III trial. We've reached an additional alignment with the FDA on the Phase III interim analysis standpoint, which allows us to start our Phase III. We intend to start by the end of this year, keeping everything on time that puts us filing at or around the end of next year. And with positive data, we hope to have this drug available for patients commercially by the middle of 2019, which is a great advance for everyone out there.

And in the process, we are, as an organization, building up through our medical affairs work, through our commercial buildup, in parallel to completing this very, very exciting Phase III trial globally.

So I'd like to first thank to Dr. Sardh for joining us. Always a pleasure, and greatly appreciate you taking the time to speak this morning. Jae, thanks again also for your contribution and for driving the Phase III program. And I'll turn it back over to Josh now.

Joshua Brodsky

All right, thanks, Jeff. And I should also mention that the replay and slides will be posted on the Alnylam website later today at alnylam.com/capella, and the transcript will follow shortly thereafter. This concludes our RNAi Roundtable for today. Thank you, everyone. Have a great day. Goodbye.
