04-Aug-2021

Alnylam Pharmaceuticals, Inc. (ALNY)

Givosiran Update Call

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MANAGEMENT DISCUSSION SECTION

Joshua Brodsky

Senior Director-Investor Relations & Corporate Communications, Alnylam Pharmaceuticals, Inc.

Good afternoon and thank you for joining us for this RNAi roundtable. Today, we'll be discussing givosiran for the treatment of acute hepatic porphyria. I'm Josh Brodsky, Senior Director of Investor Relations and Corporate Communications at Alnylam. With me today are Akin Akinc, General Manager of the Givosiran Program; Marianne Sweetser, Senior Distinguished Fellow in Clinical Development; and Laurent Placidi, Senior Director of Global Marketing for Givosiran.

Today's RNAi roundtable is the third in a series of roundtable webinars, but we're hosting this summer and fall to review progress across our various programs. Today's event is expected to run approximately 60 to 75 minutes. Akin will moderate the 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 typing your question in the ask-a-question field. Finally, as a reminder, we'll be making forward-looking statements during this webinar and we encourage you to read our most recent SEC filings for a more complete discussion of risk factors.

And with that, I'll now turn it over to Akin.

Akin Akinc

General Manager-Givosiran, Alnylam Pharmaceuticals, Inc.

Thank you, Josh. My name is Akin Akinc and I'm the General Manager for the Givosiran Program. I'm going to kick off with a brief introduction and overview of RNAi therapeutics generally and GIVLAARI, which is the trade name for givosiran specifically, before handing off to Dr. Marianne Sweetser, who will go through some of the clinical data.

RNAi therapeutics are a new class of innovative medicines that have been clinically and now increasingly commercially established as an approach with transformational potential across a variety of different disease states. They're based on Nobel Prize winning science with the ability to theoretically silence any gene in the genome. Specifically designed and synthetically produced siRNAs form the basis for RNAi therapeutics, which when introduced inside the body, engage the endogenous RNAi machinery to specifically target and modulate the levels of in a reversible and dose dependent manner proteins involved in human disease. RNAi is a potent and durable mechanism of action and has served as a product engine for sustainable innovation for Alnylam. Today, there are multiple products based on RNAi that are impacting patients globally.

On this slide is shown Alnylam's pipeline of products that have reached clinical or commercial stage. Our programs have been focused in four strategic therapeutic areas: genetic medicines, cardiometabolic diseases, infectious diseases, and CNS or ocular diseases. Four RNAi therapeutics, ONPATTRO, GIVLAARI, OXLUMO and Leqvio, through our partner Novartis, have received marketing approvals. The focus of today's RNAi roundtable is GIVLAARI, which was developed for the treatment of acute hepatic porphyria.

GIVLAARI is approved in multiple territories including the US, EU, Brazil, and Japan. GIVLAARI was first approved in the US in November of 2019 and most recently approved in Japan in just June of this year. There is continued progress with the GIVLAARI global launch with some recent second quarter highlights shown on this slide. GIVLAARI global revenues were $31 million in Q2, which represents 24% quarter-on-quarter growth. There were over 270 patients on commercial GIVLAARI at the end of Q2, showing significant growth in the quarter and continuing a trend of increasing patients on commercial therapy. In terms of highlights from the US, the largest market for GIVLAARI, there was significant growth in the quarter which was driven by net new patient adds. The prescriber base continues to expand with new writers from both community centers and centers of excellence.

Now, switching gears, I'll provide a little background on acute hepatic porphyria and givosiran. Acute hepatic porphyria or AHP refers to a family of rare genetic diseases with significant disease burden. AHP is characterized by severe potentially life-threatening attacks and chronic manifestations that negatively impact quality of life. It affects predominantly women, about 80% of the patients are women, typically in the third or fourth decade of life and given both lack of disease awareness and the range of non-specific disease manifestations, patients often suffer for many misdiagnoses on the path to an eventual AHP diagnosis.

We estimate that there are approximately 3,000 patients who have already been diagnosed in the US and Europe who have active disease. AHP is caused by a deficiency in one of the eight enzymes in the heme biosynthesis pathway in the liver, which is shown on the right side of this slide. In purple boxes, you can see the four AHP subtypes with acute intermittent porphyria or AIP, the most common type representing roughly 80% of AHP patients arising from a mutation in the hydroxymethylbilane synthase or HMBS gene. Induction of ALA synthase one or ALAS1, the first and rate limiting enzyme in the pathway, in the background of a deficiency and a downstream enzyme leads to an accumulation of upstream pathway intermediates notably ALA and PBG. Accumulation of these toxic heme intermediates is believed to be causal and responsible for AHP disease manifestations. Patients with AHP can experience acute neurovisceral crisis typically referred to as attacks which commonly manifest as severe abdominal pain and can be life-threatening if not properly treated.

In addition, many patients experienced debilitating chronic symptoms between attacks and patients with AHP are increased risk for developing hypertension, chronic kidney disease, and liver disease. Finally, not unlike other severe genetic diseases, disability, diminished quality of life, and social isolation are common in patients who have recurrent attacks with AHP.

The mechanism of action for givosiran is shown on this slide. Givosiran is a subcutaneously administered GaINAc-conjugated siRNA that targets ALAS1 mRNA in hepatocytes through RNAi. As described before, induction of ALAS1 results in accumulation of the toxic intermediates ALA and PBG which are associated with attacks and other disease manifestations of AHP. Givosiran reduces ALAS1 mRNA in the liver which in turn leads to a reduction in the levels of ALA and PBG, thereby ameliorating disease.

As mentioned, givosiran was first approved in the US under the trade name GIVLAARI for the treatment of adults with acute hepatic porphyria. Important safety information for GIVLAARI included contraindication for those with severe hypersensitivity to givosiran. Warnings and precautions include anaphylactic reactions, hepatic toxicity,

renal toxicity, and injection site reactions. For a complete product information, as always, please see the full prescribing information which is also available on givlaari.com.

And with that, let me now hand off to Marianne. Marianne?

Marianne Sweetser

Senior Distinguished Fellow, Clinical Development, Alnylam Pharmaceuticals, Inc.

Thank you, Akin. Hello. I am Marianne Sweetser and I am a medical lead for the givosiran program in clinical research and development. I will now present an overview of the program and the 18-month interim data from the ENVISION study. The clinical development program for givosiran was comprehensive and included a natural history study called EXPLORE in AHP patients in order to better understand the nature of the disease and impact of AHP on patients, clinical pharmacology studies, and two main studies in patients with AHP, the Phase 2 open-label extension or OLE that provided supportive data on the long-term treatment of givosiran and the pivotal Phase 3 ENVISION study, which is described in more detail on the next slide.

The Phase 3 ENVISION study was a multi-center, multi-national study with a six-month randomized, double-blind, placebo-controlled period and an ongoing open-label extension period to evaluate the long-term efficacy and safety in givosiran. The study enrolled a total of 94 patients at 36 sites in 18 countries. Of the 94 patients, 89 had acute intermittent porphyria, the most common type, one patient had hereditary coproporphyria, two patients had variegate porphyria, and two had acute hepatic porphyria without identified mutations but were assessed as AIP based on biochemical analysis.

During the six-month double-blind period, patients were randomized one-to-one to givosiran administered subcutaneously at a dose of 2.5 milligrams per kilo every month or placebo. After the double-blind period, all those eligible patients, 93 of them, entered the 30-month OLE period and received givosiran at doses of either 1.25 milligrams or 2.5 milligrams per kilo every month. Patients who were on the 1.25-milligram per kilo regimen who experienced inadequate disease control could increase to 2.5 milligrams per kilo at or after the month 13 visit. A subsequent protocol amendment increased the dose of all patients to 2.5 milligrams per kilo.

For this study, key inclusion criteria included age of 12 years or greater, a diagnosis of AHP, at least two attacks within the prior six months, and willingness to discontinue and/or not initiate human prophylaxis. The primary endpoint of the study was the annualized rate of composite attacks known as AAR. Composite attacks are specified as porphyria attacks that required hospitalization, an urgent healthcare visit, or hemin administration at home in patients with AIP. Secondary endpoints included levels of ALA and PPG, hemin use, the AAR in AHP patients over the six-month period, pain, fatigue, and nausea scores, and the physical component summary of the short form health survey 12 item. Exploratory endpoints included quality of life measures such as the porphyria patient experience questionnaire or PPEQ and analgesic use.

Baseline demographics and disease characteristics were generally balanced across the placebo and givosiran groups. In the study, the mean age of patients was 38 years. 90% were female and 95% of patients had AIP. The median time since diagnosis was 6.55 years and 40% of the patients were on prior hemin prophylaxis. The median historical AAR was eight with a range of zero to 46. 52% of the patients had chronic symptoms between attacks and 29% of patients used opioids daily or in most days between attacks.

As can be seen in the figures on this slide, treatment with givosiran led to a rapid and sustained reductions in both urinary ALA and PPG levels through and beyond month 18 with median reductions from baseline ranging from 82% to 94% for ALA and 76% to 95% for PPG. During givosiran treatment, the majority of patients achieved near normalization or normalization of ALA and PPG levels.

Long-term treatment with givosiran resulted in a sustained reduction of attacks and the patients treated with givosiran. During both the double-blind and OLE period, the AAR remained low. In these continued givosiran patients, the median AAR was 1.0 and zero during the six-month double-blind and OLE periods respectively.

In the placebo crossover patients, median AAR decreased from 10.7 during the double-blind period to 1.6 in the OLE during givosiran treatment, an 85% reduction. Additional analyses of composite porphyria attacks over time are shown on this slide. When evaluated by three-month intervals, the average number of porphyria attacks experienced per patient showed a decrease during longer treatment with givosiran. Similarly, this was reflected by an increase in the proportion of patients with zero attacks over time during givosiran treatment. At month 18, the proportion of patients with zero attacks was 61% in the continued givosiran patients and 40% for the placebo crossover patients.

Long-term treatment with givosiran resulted in sustained reductions in hemin use that was demonstrated both by a reduction in annualized days of hemin use and a corresponding increase in the proportion of patients with zero days of hemin use. As seen in the figure on the left, median annualized days of hemin use was zero in the continued givosiran patients during both the double-blind and OLE periods. In the placebo crossover patients, the median annualized days of hemin use decreased from 15 during the double-blind period to zero during givosiran treatment in the OLE period, 100% reduction. Similarly, the proportion of placebo crossover patients was zero days hemin use increased from 26% during the double-blind to 51% during givosiran treatment in the OLE.

Patients treated with givosiran showed further improvement from baseline across the different quality of life assessments measured in the study that increased with long-term dosing. On this slide, results for the physical component summary of the SF-12 are shown on the left and the EuroQoL-visual analog scale questionnaire on the right. For both assessments, an increase in the value for mean change from baseline corresponds to improvement. As presented in the figures, the continued givosiran patients showed improvement from baseline in both assessments during the double-blind period as compared to the placebo patients and then had further increases in scores during the OLE period. The placebo crossover patients had similar improvements at month 18 during treatment with givosiran.

For the SF-12 survey, in addition to improvement in the PCS scores during givosiran treatment, a similar pattern of improvement was observed on scores for the mental component summary and across all the individual domains with the most important impact on physical, bodily pain, general health, and social functioning. Improvement in patient reported outcomes were also observed with long-term dosing. Results for the porphyria patient experience questionnaire, the PPEQ, are shown on this slide. A higher proportion of patients in the continued givosiran group reported responses of much better or always across all domains of the PPEQ during the OLE period as compared with the double-blind period.

Long-term treatment was also associated with improvements in activities of daily living, perception of treatment, and living a more normal life. A similar pattern in response was seen in the placebo crossover patients. Givosiran treatment also led to a decrease in the number of work days missed due to porphyria in the past four weeks in both patients' groups when compared with the placebo of patients in the double-blind period.

[indiscernible] (00:19:17) safety data from the first dose of givosiran to the interim data cutoff date of January 10, 2020 are shown on this slide. Mean exposure was 18.9 months for the continued givosiran patients and 13 months for the placebo crossover patients. The maximum exposure was 25.1 months. The safety profile of givosiran remained acceptable with no new safety concerns. The majority of adverse events continued to be mild-to-moderate in severity. The most common related AEs reported in at least 10% of patients were injection site

reactions, nausea, and fatigue. Serious adverse events reported in greater than or equal to 2% of patients were urinary tract infections, chronic kidney disease, and device breakage. Each of these were reported in two patients during the study. There were no deaths.

During the interim period between the data cuts at month 12 and 18, there was only one new AE of drug hypersensitivity which led to treatment discontinuation. There were no new treatment related SAEs or safety concerns regarding hepatic AEs. And as reported previously, elevations in serum aminotransferases have primarily been observed during the three to six-month period after initiation of treatment.

Renal events characterized by increases in serum creatinine and corresponding decreases in estimated glomerular filtration rate or EGFR were reported in 16 patients. There were no new renal serious adverse events and none of the renal events led to discontinuation of givosiran. Overall, small decreases in EGFR were observed early in therapy and then EGFR tended to stabilize by months 12 to 18.

In summary, treatment with givosiran showed a sustained decrease in ALA and PPG levels through and beyond month 18. Reductions in the annualized rate of composite attacks were sustained during long-term treatment with givosiran. This is further demonstrated by both a decrease in the mean number of porphyria attacks per patient and an increase in the proportion of patients with zero attacks over time. Similarly, there was a sustained reduction in hemin use both in the median annualized days of hemin use and an increase in the proportion of patients with no hemin use over time.

Givosiran treatment led to improvement in multiple measures of quality of life and reduction in work days missed due to porphyria. The safety profile remained acceptable and consistent with that previously observed. Overall, in the ENVISION study, givosiran showed a durable response and clinical efficacy across a wide range of clinical parameters during long-term treatment.

Alnylam is also committed to generating data on the real-world use of GIVLAARI. To accomplish this, we've recently launched the ELEVATE registry. ELEVATE is a perspective global observation study designed to characterize the natural history and real-world clinical management of patients diagnosed with AHP. The primary objective is to study the long-term safety of GIVLAARI in patients with AHP. Secondary objectives include the study of the real-world effectiveness of GIVLAARI in different AHP populations and the description and the natural history in real-world clinical management of patients diagnosed with AHP whether on GIVLAARI or other types of treatment.

So, thank you. I would now like to hand off to Laurent, who will go over efforts to increase disease awareness and efforts to help patients around the world.

Laurent Placidi

Senior Director-Global Marketing Givosiran, Alnylam Pharmaceuticals, Inc.

Thank you, Marianne. My name is Laurent Placidi. I'm the Global Commercial Lead for GIVLAARI. And then today, I'm going to walk you through our efforts to increase disease awareness as well as our progress towards our geographic expansion. Patients with AHP often go through a long and frustrating journey on the road to a proper diagnosis. Over the last few years, we have conducted extensive market research, interviews, as well as reviews of the identified patient charts. Through those, we have identified several trends and commonalities particularly with regards to certain symptoms, potential misdiagnosis, or comorbidities, as well as the type of physician specialties these patients could be referred to. Those include internal medicine, emergency room physicians, gastroenterologists, OB/GYNs, urologists, or psychiatrists for example. This knowledge along with the

use of artificial intelligence or AI is giving us opportunities to increase awareness of AHP among targeted HCP specialties as well in patients and provide disease information in new and different ways.

Today, I will focus my presentation on three main areas of work from our medical and commercial teams. First, data and scientific exchange including including analysis of medical and pharmacy claims as well as our activities in the area of testing. Second, use of technology particularly work done to support improved visibility of AHP testing in EMRs, electronic medical records, as well as the development of apps aimed at supporting longitudinal patient assessment and improving HCP patient communications about their disease burden. And finally, heart disease education.

Our AHP focused educational campaign has been a great success. So far, we have had over 1.5 million visits to our websites that exist in multiple languages. [ph] The specialty's (00:26:00) engaged to reflect those involved in the patient diagnosis journey that I just showed earlier.

In the US, we also have a process that allows interested HCPs to have to be connected with our field teams for more information about AHP or about GIVLAARI. This approach is now being replicated in Europe. Our extensive research and work with claims database has also allowed us to identify common misdiagnosis of comorbidities that those patients are suffering. Our medical team is now supporting research with HCPs or hospitals to initiate screening studies using these criteria of enrichments to understand if they may have a positive impact on earlier more accurate diagnosis. Some of these studies are ongoing.

Our medical team also facilitated panels, commercial laboratories, as well as AHP clinical experts to develop recommendations for publication on biochemical diagnosis of AHP. This manuscript was published earlier this year. From an access and ease of testing point of view, we are pleased to share that a rapid urinary porphobilinogen test kits developed by Teco Diagnostics without supports was cleared for use by the FDA this week. These test kits will allow for the identification of elevated UPBG in approximately 30 minutes instead of an often much longer turnaround currently. The pandemic has highlighted to us the importance of third-party led education. We're currently running several programs across the globe.

In the US, partnerships with Medscape and Doximity has allowed us to bring AHP education to several thousands of HCPs including to some specialties we're not engaging directly via our field teams. We have also initiated a triggered e-mail program based on the type of content these HCPs are searching on certain online journals, like searches on porphyria or givosiran or other relevant keywords. In Europe, we partnered with a company called PeerVoice, who has access to a large network of different specialties and have launched several specialty specific programs tailored at increasing AHP signs and symptoms recognition with the right audience.

The program has so far been very successful with over 35,000 meaningful interactions which we define as the time spent by the HCP interacting with the program, which we feel is more important than just measuring [ph] click rates (00:28:39). It has been demonstrated that with the growing adoption of electronic health records over the last decades, new opportunities exist for leveraging EHR data for detection of rare diseases. In this case, our medical colleagues partner with physicians from Oregon Health to analyze that EHR records and see whether we could identify patients who had not been previously tested for porphyria. The output was very interesting. Not only did the collaborative research resulted in identifying 30 patients who were unknown to the investigator, but also a significant number of patients believed to have AHP.

Some of them were slags based on the review of the physician notes and an additional 18 presenting with signs and symptoms of the disease and have never been tested for AHP or were never suspected to have AHP. These patients would possibly benefit from AHP testing. We're continuing to offer a third-party genetic testing and

counseling program called Alnylam Act. As a reminder, the program was developed to reduce barriers to genetic testing and counseling and to help people make more informed decisions about their health.

Genetic testing and counseling is offered at no charge to individuals who meet the eligibility criteria. Genetic testing is available in the US as well as certain other countries. Genetic test counseling is only available in the US. As of July, we've had almost 1,000 participating HCP accounts, over 1,800 samples were submitted for testing, and thus far the program has identified 180 patients with a positive AHP mutation. As I mentioned in the patient journey slide, prospective patients are searching for answers online or in social media. With the support of several AHP patients worldwide, we built a campaign and patient-facing websites with lots of relevant education about AHP.

Right now, our websites are available in many languages and our team are continuing to expand its suffering to new markets. As you can see the numbers are quite impressive. In the US, approximately 7,000 self-identified patients have signed up for information. We know that the majority of the other individuals probably do not have AHP, because many of the symptoms are also similar to more common illnesses. But our goal is really to create awareness ensuring AHP is discussed and potentially excluded from the diagnosis. Ultimately, the physician makes the diagnosis and we're hoping that our education allows them to consider AHP when and where appropriate and relevant. On the US website, any interested individual can also request connect with one of our field-based patient education liaisons and so far this year, we've had over 50 interest individual requests in such a meeting. I would say that 80% of them are undiagnosed individuals interested in hearing about AHP and the rest were currently diagnosed patients.

Social media can also be an important tool for patients seeking disease information and this example we partner with Facebook health communities in the US, specifically those with individual suffering from abdominal pain. Their approach is relatively simple. We posted an ad and allowed the interested individuals to click on it and take a survey about their pain. Since the beginning of the program, over 56,000 individuals have taken the survey. Interestingly, when you asked the respondents about their other symptoms around their spin attacks, over 1,300 also noticed reddish brown urine and 2,200 also have skin sensitivity or blistering. Obviously, these two symptoms are very common in AHP.

These individuals are then offered to sign up for additional information and directed to talk to the doctor. Among the individuals who have had signed up for information, we have noticed that over 1,200 have downloaded our patient doctor discussion guide about AHP. It is important to note that we have no means nor any desire to track whether these individuals get tested or not.

Our team also felt it was important to tell the story to broader audiences to help raise awareness of AHP. Here are our two recent approaches using prints and TV, both supplemented by social media and digital. We have partnered with AHP patients to share their stories. These articles were published in two popular outlets, littlethings.com and [ph] catchyourmom.com (00:33:26). In a very short period of time, we have over 720,000 views of these articles.

In another opportunity during International Porphyria Awareness Week last April, we supported a popular segment on Lifetime TV called Behind the Mystery, where Nicole, an AHP patient ambassador for Alnylam and Dr. Erwin, a porphyria expert, who together shared their personal and clinical perspectives on AHP. This segment attracted over 700,000 viewers.

We also believe that patient identification is not just about supporting diagnosis, but also providing tools, education, and the ability for currently diagnosed patients to have a better communication with the care team. The

app we're developing is an example on how technology can also be used to support identification of patients who may benefit from treatment. This app is called My Porphyria app and includes a symptom tracker, surveys or electronic patient reported outcomes, performance tests, and also the ability for patients to invite treating HCP to access the data. We have had multiple interactions with experts in AHP as well as patients and patient groups around the world to ensure that the app was relevant and helpful. We've received some great feedback and support for the project and are currently working on a pilot in Germany and are hoping to launch it by the end of the year.

In summary, understanding the patient journey has been critical in guiding our efforts and activities. And I hope you can appreciate that we have developed many initiatives to support this goal on the AHP community. Most importantly, we're excited with the results our medical and commercial teams have achieved and the best illustration is their quotes from the patient who reached out to us via one of our platforms. That patient said, after dealing with this my whole life and almost giving up on ever finding a diagnosis, your video is the only one that I have ever fully related to. Without your video, I would have given up and continued to suffer. Now, I am in the process of getting a referral to hematologists.

Patient identification is obviously critical to our ability to help patients. In addition, expanding our geographic footprint is also extremely important in order to help other patients around the world. In addition to the US, our launch in Germany is going very well with great access to GIVLAARI. Similarly in Italy, we have received innovation status that allows us to serve a large group of patients in need. In France and other countries, we continue to have name patient sales. We also got approval in Japan recently as well as Canada, Switzerland, and Israel. For the rest of the year, we will continue to execute on our planned global regulatory filings and launches across many regions.

In June of this year, we had received JNDA approval for the treatment of AHP in adults and adolescents aged 12 years and older. We are truly excited about bringing GIVLAARI to patients in Japan and I wanted to briefly discuss the dynamics in Japan as well as touch on our launch preparation activities. We believe there is an estimated 1,000 AHP patients with active disease in the country. ALA and PPG biochemical tests are reimbursed and some academic centers offer genetic testing as well. Our team is currently working hard on the launch activities including analyzing claims database, improving disease awareness, and engaging with both KOLs and patient association groups.

Now, I'll turn back to Akin for closing the call. Thank you.

Akin Akinc

General Manager-Givosiran, Alnylam Pharmaceuticals, Inc.

Thanks, Laurent. Just to summarize, I think we're obviously very excited. We think GIVLAARI represents a treatment option for patients with AHP which is a rare disease with significant burden. The 18-month ENVISION open-label extension data demonstrate GIVLAARI's long-term efficacy and safety profile. We're pursuing global multi-channel initiatives to improve AHP disease awareness. Laurent talked about those, those include applying digital tools to promote education, leveraging AI and data-driven approaches where we can, utilizing media platforms to ensure an even broader reach.

The GIVLAARI launch is ongoing in the US with select EU countries. We haven't talked about it too much today but we know as with our other medicines at Alnylam, we're really employing a value-based philosophy to facilitating broad access to our medicines which we believe is so important. And obviously, continued geographic expansion is going to be an important driver of growth for GIVLAARI and we're very excited in that regard about Japan as really representing a key new market.

So, with that, I think we're now going to turn to some Q&A and take some questions.

QUESTION AND ANSWER SECTION

Akin Akinc
General Manager-Givosiran, Alnylam Pharmaceuticals, Inc.

A

Maybe I'll first start with a question now for Marianne. Can you say a little bit more about the one patient who discontinued treatment due to an AE between the 12-month data cut and the 18-month data cut?

Marianne Sweetser
Senior Distinguished Fellow, Clinical Development, Alnylam Pharmaceuticals, Inc.

A

Yes, I can. Good question. There was one patient who discontinued treatment due to this adverse event of drug hypersensitivity and that was considered related to study drug by the investigator. The patient had a medical history of asthma, drug hypersensitivity to opioids and other drugs, and multiple allergies including food, seasonal, and arthropods. The patient also had elevated tryptase elevations at baseline. This was not an anaphylactic reaction and do not require any hospitalization, it's not a serious event.

Akin Akinc
General Manager-Givosiran, Alnylam Pharmaceuticals, Inc.

A

Thanks, Marianne. Maybe another question, this is a little bit maybe detailed in terms of the data, but the proportion of placebo crossover patients without attacks was lower than that on the continued givosiran patients at month 18. Do you have any speculation why those patients might have been different or what might have led to that difference?

Marianne Sweetser
Senior Distinguished Fellow, Clinical Development, Alnylam Pharmaceuticals, Inc.

A

Thank you. Well, as we saw in the presentation that the proportion of patients in the ENVISION study without attacks has shown an increase over time with longer treatment. So, when you compare the continued givosiran patients who had on average at least six months additional treatment compared to the placebo patients, it is possible that could attribute to the difference. So, therefore, with longer treatment, this apparent difference may go away and we will be looking soon at the 24-month data that will be presented at the upcoming conference and that may help answer the question.

Akin Akinc
General Manager-Givosiran, Alnylam Pharmaceuticals, Inc.

A

Thanks, Marianne. Now, a question for Laurent. How has diagnosis of AHP changed since approval of GIVLAARI and have you been able to notice an increase of awareness and diagnosis of patients?

Laurent Placidi
Senior Director-Global Marketing Givosiran, Alnylam Pharmaceuticals, Inc.

A

So, market research we conducted on targeted specialties that I've shown in my first slide show an increase in understanding, recognition, and knowledge of the tests, but also the sign and symptoms and at par informing diagnosis. That suggests our efforts are really helping physicians to diagnose patients. [ph] There are already (00:41:27) two main opportunities to diagnose patients including those with less severe phenotype. You can do it

during an attack while they're being cared for in an ER or hospital setting as well as during HCP patient interactions often driven by chronic unexplained symptoms. In both cases, disease education is critical particularly for physicians involved in patient diagnosis journey. Within that context, our education efforts aim to spread awareness of all signs and symptoms including acute attacks and also as importantly chronic symptoms. More specifically, we're leveraging virtual tools, social media for HCP education. These include all our websites as well as a number of initiatives underway and are reaching [ph] HCPs (00:42:13) on virtual platforms like Medscape and Doximity.

Akin Akinc
General Manager-Givosiran, Alnylam Pharmaceuticals, Inc.

A

Thanks, Laurent. Maybe we'll switch gears here. This question here about ELEVATE and this I'll kick over to you, Marianne. The question is you have included efficacy assessments in the study and will be enrolling patients on GIVLAARI and other treatments. Is there really any plan for informal long-term comparisons across different treatments?

Marianne Sweetser
Senior Distinguished Fellow, Clinical Development, Alnylam Pharmaceuticals, Inc.

A

So, as we said before, ELEVATE is an observational study and it's not really designed for any cross-treatment comparisons. We're allowing the enrollment of patients who are on other therapeutics or are no therapy in order to describe the natural history and the real-world clinical management in patients diagnosed with AHP. But it's not powered – it's only descriptive and it's not powered to be able to make these long-term comparisons.

Akin Akinc
General Manager-Givosiran, Alnylam Pharmaceuticals, Inc.

A

Understood. Maybe back to Laurent, a question here about screening studies. What kind of screening studies have you conducted to-date and is there anything you can say about any results from those studies?

Laurent Placidi
Senior Director-Global Marketing Givosiran, Alnylam Pharmaceuticals, Inc.

A

So medical team had several ongoing screening studies, including investigator-initiated studies and research collaborations. As an example, we're running studies looking at cyclical vomiting syndrome which based on data is thought to be comorbidity in up to a quarter of those patients. Similarly, we're running screening studies for POTS, which is postural orthostatic tachycardia syndrome, which is another potential comorbidity in AHP patients. We also have similar projects in the area of gastroenterology as well as neurology. Such studies in likely enriched population will hopefully contribute to the body of knowledge about the disease and we're looking forward to seeing the results.

Akin Akinc
General Manager-Givosiran, Alnylam Pharmaceuticals, Inc.

A

Thanks, Laurent. And maybe going back to you, Marianne, on ELEVATE. This is a registry, but do we have plans to present data from ELEVATE? And what would that look like and when might we see some data?

Marianne Sweetser
Senior Distinguished Fellow, Clinical Development, Alnylam Pharmaceuticals, Inc.

A

So yes, we definitely plan to share data at an appropriate medical or scientific forum in the future. Currently, it's premature to speak about when we might do this as we just initiated the study. So, we're in the process of initiating sites and patients are just starting to enroll.

Akin Akinc
General Manager-Givosiran, Alnylam Pharmaceuticals, Inc.

A

Thanks, Marianne. Just one or two more questions left here. I'm going to – and I think they're both to you, Laurent. First one here is, what are highlights that we should look forward to for GIVLAARI in international markets through the remainder of the year?

Laurent Placidi
Senior Director-Global Marketing Givosiran, Alnylam Pharmaceuticals, Inc.

A

So, we've now launched in Germany and Italy and have name patient sales in other countries including France and a [ph] cohort eight-year program (00:45:22). We also expect to finalize pricing and reimbursement in all the key markets in Europe by the end of the year. In addition, as mentioned in one of our slides, we received approval in Japan this past June and I'm very excited about bringing this therapy to patients in Japan.

Akin Akinc
General Manager-Givosiran, Alnylam Pharmaceuticals, Inc.

A

Thanks, Laurent. And maybe just last question just following up on that, should we be expecting revenue out of Japan this year or is it too early?

Laurent Placidi
Senior Director-Global Marketing Givosiran, Alnylam Pharmaceuticals, Inc.

A

Yeah, we can expect to achieve reimbursement in Japan in the second half of this year and we'll be launching shortly thereafter.

Akin Akinc
General Manager-Givosiran, Alnylam Pharmaceuticals, Inc.

Okay. Great. Well, I think that wraps it up for this roundtable and just to kind of put this on everyone's calendars, we hope you enjoyed today's roundtable on GIVLAARI. We also hope that you can tune into Alnylam's next RNAi roundtable which is going to be Thursday, August 19th at 9:30 AM Eastern Time for a discussion of lumasiran for the treatment of primary hyperoxaluria type 1. So please go to the Capella section of Alnylam's website for more information. Thank you.

Operator: This concludes the call. You may now disconnect.