Alnylam Pharmaceuticals Inc "RNAi Roundtable" Webcast Series: Patisiran & Vutrisiran, in Development for the Treatment of Transthyretin-Mediated Amyloidosis

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PRESENTATION

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

Good afternoon, everyone. Thank you for joining us today for this RNAi Roundtable, where we'll be discussing patisiran and vutrisiran development for the treatment of transthyretin-mediated amyloidosis. I'm Christine Lindenboom, Senior Vice President of Investor Relations and Corporate Communications at Alnylam.

With me today are Eric Green, Senior Vice President and General Manager of the TTR program; John Vest, Vice President of Clinical Research; Rena Denoncourt, Senior Director and Program Leader of the vutrisiran program; and Dr. Nitasha Sarswat, Director of the Infiltrative Cardiomyopathy Program at the University of Chicago Hospital.

Before I hand it over to Eric, I'll start with a few brief comments. Today's RNAi Roundtable is the fourth in a series of roundtable webinars that we've been hosting over the past few months to review progress across our various programs. Today's event is expected to run approximately 75 minutes. Eric will moderate a Q&A session at the conclusion of the presentation. If you'd like to submit a question, you could do so at any time during the event by typing your question in the ask a question field.

Finally, as a reminder, we will be making forward-looking statements during this webinar and encourage you to read our most recent SEC filings for a more complete discussion of our risk factors.

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

Eric Green, Alnylam Pharmaceuticals, Inc. - VP and General Manager of TTR Program

Thank you, Christine, and thanks to everyone for joining us today to hear about our TTR program. I'll make a few introductory comments, but quickly dive into the focus of today's presentation. In particular, I am pleased to have Dr. Sarswat join us today to present her experience with the treatment of patients with ATTR amyloidosis.

RNAi -- sorry, Alnylam is the leading RNAi therapeutics company, committed to advancing a whole new class of medicines for a wide range of human diseases. Based on Nobel Prize winning technology, we can essentially silence any gene in a human genome. With this elegant and natural mechanism, we can significantly reduce disease-causing proteins or toxic metabolites that contribute to the clinical manifestations of various conditions. At Alnylam, we have successfully harnessed the RNAi mechanism to build an organic product engine to deliver sustainable innovation and to bring medicines to patients with high unmet medical need around the globe. We truly believe this underscores the transformational potential of this modality as a whole new class of medicines.

Turning now to Alnylam's pipeline of commercial and late-stage development programs, you will see, we are focused on 4 Strategic Therapeutic Areas, or STArs. These include genetic medicines, cardiometabolic diseases, infectious diseases and CNS or ocular diseases. Presently, we have 2 approved products ONPATTRO and GIVLAARI, the latter for the treatment of acute hepatic porphyria; 2 additional products, lumasiran, for the treatment of primary hyperoxaluria Type 1 and inclisiran for the treatment of hypercholesterolemia are both currently under review by various regulatory agencies. We currently have 6 programs in Phase I or Phase II clinical development. Overall, we expect our organic product engine to deliver sustainable innovation with 2 to 4 INDs per year. If you're interested in learning more about any of these programs, I recommend listening to our RNAi Roundtable from July 17 that focused on our early-stage pipeline.

Today, we will focus on our TTR programs ONPATTRO and vutrisiran. ONPATTRO is currently approved in numerous countries for the treatment of hATTR amyloidosis with polyneuropathy, with specific indications and labels vary by country. We also have additional clinical development ongoing for patisiran, the nonproprietary name of

ONPATTRO, for a potential label expansion as well as a robust clinical development plan for vutrisiran. ATTR amyloidosis is a rare progressively debilitating disease caused by misfolded TTR protein that accumulates as amyloid deposits in multiple tissues, including the heart, nerves and GI tract. Both the hereditary and wild-type forms of the disease may present in adults with multisystem involvement and a high burden of disease that is often fatal. As with most rare diseases, the true prevalence is difficult to know. But we believe there are approximately 50,000 patients worldwide with the hereditary form of the disease where the patient carries a mutation in their TTR gene.

In certain regions, there are countries that are endemic populations given the autosomal dominant nature of the disease. Patients without a TTR mutation can also accumulate misfolded TTR protein in tissues, often associated with advancing age, leading to wild-type ATTR amyloidosis. Prevalent estimates for this patient segment are significantly larger, perhaps 200,000 to 300,000 patients worldwide, though some estimates are much higher. In both cases, patients can present with a variety of symptoms, as shown on the right side of the slide.

Our therapeutic hypothesis is quite simple, utilize an RNAi therapeutic to dramatically reduce the production of the disease-causing TTR protein in the liver, preventing continued amyloid deposition and allowing the body to potentially remove existing deposits, ultimately halting or improving the manifestations of the disease. This hypothesis follows logically from the historical treatment intervention, a liver transplant, which removes the production of the variant or mutant TTR protein but replaces it with continued production of wild-type TTR protein from the new liver. Other treatment modalities attempts to interfere with the disease cascade at later points well after the TTR protein has been made and is circulating throughout the body. We strongly believe that suppressing the production of both variant and wild-type TTR protein is the best way to treat the disease.

As noted earlier, we have 2 RNAi therapeutics in our portfolio, ONPATTRO and vutrisiran. ONPATTRO was first approved in the U.S. in August 2018 for the treatment of the polyneuropathy of hATTR amyloidosis based on a landmark APOLLO Phase III study. ONPATTRO is administered by IV once every 3 weeks. Vutrisiran is our investigational RNAi therapeutic targeting TTR that utilizes our ESC GalNAc-conjugate chemistry to deliver a very compelling profile, simple subcutaneous administration of a low-volume product from a prefilled syringe at 25 milligrams once every 3 weeks -- sorry, once every 3 months, very critical difference. Additionally, based on our Phase I data at higher dose levels and additional remodeling work, we are also exploring an additional 50-milligram biannual dosing regimen. Vutrisiran is being evaluated in the Helios clinical program across the full range of patients with ATTR amyloidosis, and we'll get into more into those details shortly.

ONPATTRO was the first ever RNAi therapeutic to be approved with initial approvals in the U.S. and EU just over 2 years ago. And since then, we have continued our global commercial expansion with additional approvals in Canada, Japan, Switzerland and most recently, Brazil. The launch of ONPATTRO has gone very well with greater than 20% revenue growth quarter-over-quarter through Q1 of this year. The Q2 results were impacted by COVID-19 in some key markets but saw continued strong growth from our international markets. This represents the benefit of a global business and validates our decision to build a global, fully integrated business. As of the end of Q2, we had over 1,050 patients on commercial ONPATTRO around the world, demonstrating steady continuous growth of new patient starts, even in the face of a global pandemic in Q2.

In just under 2 years since approval, we have gained market access in all big 5 Western European markets as well as Portugal, Sweden, the Netherlands and Belgium. This reflects great work by our market access and country teams, but also the strength of the APOLLO data and is much faster than what most orphan medicines are able to achieve. And as expected, Japan became the second largest market for ONPATTRO, by revenue, in Q2. We are very pleased with the commercial launch of ONPATTRO and would refer everyone to our most recent quarterly results from August 6 for additional details on our recent commercial activities.

At the PNS virtual event earlier this summer, we presented 2 important new datasets. On the left of the slide is the 2-year data from the global OLE study, or open-label extension, specifically the impact of continued treatment with patisiran on mNIS+7, a measure of neuropathy impairment. The blue line shows continued improvement relative to the original APOLLO study baseline for patients treated with patisiran for 42 months, that is the 18 months on APOLLO and the additional 24 months in the global OLE study. The patients who received placebo treatment in APOLLO, the red line, showed a market worsening for the first 18 months, but have demonstrated a halting of their neuropathy impairment switching to patisiran in a global OLE. Unfortunately, the impairment that they accumulated during APOLLO, while on placebo, can't be fully overcome, further stressing the importance of early diagnosis and initiation of a treatment that has the potential to halt or reverse the polyneuropathy symptoms of hATTR amyloidosis. Importantly, patisiran continues to show a positive benefit risk profile with additional exposure, with some patients having received over 6 years of continuous patisiran treatment.

On the right side, we presented interim data from our study of patisiran in patients who have experienced disease progression after an orthotopic liver transplant or post-OLT. Consistent with data from APOLLO, we see a rapid and substantial mean reduction in serum TTR after a single infusion that is maintained during 6 months of continued treatment with patisiran. The mean reduction of serum TTR was nearly 90%. As noted earlier, these patients have donor livers that are expressing wild-type TTR, but patisiran was designed to silence both variant and wild-type TTR. To date, the safety profile of patisiran in this population remains consistent with the APOLLO Phase III study.

Today, we are primarily focusing on ATTR amyloidosis with cardiomyopathy, but a quick reminder of a very important study for us, HELIOS-A. We completed enrollment in this study earlier this year just before COVID-19 hit most countries. We enrolled a little over 160 patients with hATTR amyloidosis with polyneuropathy, with the primary endpoint as the change in mNIS+7 from baseline after 9 months of treatment. We're expecting top line results in early 2021. Our team has been diligently supporting patients and our clinical sites during COVID-19, focusing on continued dosing on schedule, completing study assessment visits and insurance study data quality. Particularly given the unprecedented burden that the pandemic has placed on the healthcare system, the simple and infrequent dosing regimen of nutrition was highly beneficial in maintaining patients continuity of treatment on study.

I now have the pleasure to introduce Dr. Nitasha Sarswat. Dr. Sarswat is a board-certified cardiologist, specialized in heart failure, with a particular expertise in cardiac amyloidosis. She is the Director of the Infiltrative Cardiomyopathy Program at the University of Chicago Hospital. We have invited Dr. Sarswat to provide her perspective as a treating physician in the field. Thank you for joining us today, Dr. Sarswat. I'll hand it over to you.

Nitasha Sarswat,

Thanks, Eric, and thank you for inviting me to speak about something that's very important to what I do on a daily basis. So again, as you said, I'm an advanced heart failure and transplant cardiologist at University of Chicago. I initiated and run our amyloid program.

Next slide. For the goals of the discussion for today, what I want hit -- really hit home: first, cardiac amyloidosis is more prevalent than what we initially thought; second, it's very challenging to diagnose. Therefore, all physicians, all health care workers must have a high index of suspicion. Cardiac amyloidosis carries a high morbidity and mortality and time to diagnosis and treatment is essential. The field is exploding at an amazing pace given new diagnostic tools and the emergence of new therapies. It's been very exciting time to be part of this field. Treatments are now available for all types of cardiac amyloidosis, and I really want to hit home that it's imperative to understand which subtype is involved in order to effectively treat the appropriate type of amyloidosis.

Next slide, please. I'm going to start with a patient case. This is a patient who I've known for about 5 years. She is a 53-year-old African-American female with a past medical history of hypertension and a family history of heart failure. Her father actually passed away with cardiogenic shock around the time shortly before I met her. She presented to my clinic with worsening dyspnea during her Zumba classes. And when she came to clinic, I found that she was in decompensated heart failure, and I admitted her to our inpatient service for diuresis and fluid removal.

Next slide. Just to show the very first thing, we did a 2D echocardiogram of her heart and these are still-pictures, not movie. But what you can see in the upper left-hand is the left ventricle, the striking thing is that the ventricle is very thick and has that classic sparkly myocardia. The actual LV cavity, where the blood fills the left ventricle is actually on the small side. When you look at the picture on the upper right-hand side, similarly, you get the sense that the left ventricle is extremely thick. And then on the bottom picture, in the apical 4 chamber, again, the intraventricular septum is very big and hypertrophied. The LV and RV cavities are both very small; and both atria are very big and dilated, and volume-wise, actually larger than the ventricle. This is a classic look for infiltrative cardiomyopathy.

Next slide. So at the point, after meeting her, again, as an inpatient, we had a pretty high suspicion for infiltrative disease. We went back to the patient and because we're cardiologists, we don't often ask about these questions initially. We went back and asked her a few more questions, which revealed that she actually has a history of bilateral carpal tunnel syndrome. She had chronic diarrhea and had about a 10 pound overall weight loss in the last 6 months. At that point, as the next diagnostic assessment, we sent her for a cardiac MRI.

Next slide. This is 1 view of her cardiac MRI, but what you can see is that there is diffuse subendocardial enhancement of both the left ventricle and the right ventricle. Again, classic for cardiac amyloidosis from what we expect to see that the gadolinium is taking up the amyloid fibrils, and it certainly raises our suspicions even higher.

Next slide. Again, on apical 4, we see diffuse enhancement of the septum, sub-endocardium. We can see enhancement of the intraatrial septum, atrial walls. We see classic pleural effusion as well as pericardial effusion.

Next slide. Facts of our case. Again, at this point, our suspicion was not only for the infiltrative cardiomyopathy but specifically more for cardiac amyloidosis. We sent some basic lab work to help rule out AL amyloidosis, that's a serum protein electrophoresis, a urine protein electrophoresis and immunoglobulin light chains, all of those returned and were normal. At that point, our diagnosis was pointing more towards TTR amyloidosis. We ordered a PYP scan, which shows grade III uptake in the heart, and we were able to avoid a myocardial biopsy.

Next slide. At this point, we felt like she was more -- most likely to have TTR amyloidosis. And then became the decision on the decision tree as whether or not she had hereditary or wild type. We sent a TTR genetic test. As an inpatient, we continued to diurese her and she had worsening renal function as we often see. We did a right heart catheterization, which showed a restrictive filling pattern. Again, just classic as we remove fluid, the renal function gets worse in restricted filling. We ended up diuresing her guided by a swan-ganz catheter. Her volume status eventually stabilized and her renal function improved, and we were able to discharge her to home.

Next slide. Since that time, she's been followed closely in our amyloidosis clinic. Her genetic test resulted within a few weeks, and she was found to have a valine-isoleucine mutation with nearly 122 high mutation. We did a long genetic counseling with her, and we have screened her entire family. She's currently on both tafamidis and patisiran therapy. Her intracardiac pressures have been followed closely with CardioMems, and she's been able to resume her Zumba classes.

Next slide. So why did I choose this case to tell you about cardiac amyloidosis? I think there are a couple of really important points. The patient was able to turn around quickly and survive and had a good quality of life, once we recognize what her disease was, once we recognize the hemodynamics that were at play. The second thing is that we were able to use novel imaging technique in the PYP, which allowed an essentially noninvasive diagnosis. And the third is that new therapies were able to be offered to the patient to attack the disease from multiple venues, which is different certainly than what I was able to offer 4 or 5 years ago. Now we actually have therapy. So this offers a new hope for patients just like her.

Next slide. I wanted to talk a little bit about the pathophysiology of TTR amyloidosis. So as Eric alluded to, what we have seen in TTR amyloidosis is normally the TTR protein is a tetramer, similar to a (inaudible). What happens is when that (inaudible) disintegrates into individual (inaudible) and then those (inaudible) all conglomerate together and can deposit in multiple places as a toxic deposit of an amyloid fibril. That transthyretin protein is a necessary function in our body and serves as a transporter protein for thyroxin and retinal-binding protein.

Next slide. When we do do biopsies, what do we expect to see on the pathology? So on the left here on the slide what we see is an H&E stain. And all of that pink and fluffy material is actually amyloid deposits that are distorting the architecture of the normal myocardia. On the right, we see, what's called a Congo red theme and we see this classic apple-green birefringence, which is again has a pneumatics for cardiac amyloidosis. Now the important thing to understand here is that at this point, if we do do a biopsy, it's very important to send this for mass spectroscopy, which offers the greatest sensitivity and specificity for subtypes.

Next slide. Now this is important because the different types of cardiac amyloidosis protend a different prognosis, and this is a very important in terms of counting our patients. So this type of chart is exactly what I showed to my patients when I see them in clinic. We tell them that amyloidosis is a systemic disease that can often present as an infiltrative cardiomyopathy. And when we talk about the different kinds of amyloids, AL amyloid protends the worst prognosis. Unless untreated is about a 6- to 9-month survival. AA amyloid very much depends on the underlying disease, whether its rheumatoid arthritis or tuberculosis. And then TTR amyloid, as we've talked about, is divided into 2 different types, both hereditary or familial and senile or wild type, and the prognosis is dictated by the subtype. Now this data in terms of the mortality is based on previous lack of treatment. What we don't truly know is what is the mortality from the cardiac perspective with new and modern treatment.

Next slide. We also don't know if TTR fibrils are truly toxic to the heart or if they were just distorting the architecture. We do know that with other types of amyloid that they truly are toxic, but it is not clear in TTR, if that is still the case.

Next slide. There are several staging systems that we can help to guide our patients and what to expect as time goes. So this is an initial staging system that was made by Dr. Grogan at the Mayo Clinic, who is one of my heroes. And certainly, 1 of the 2 biomarkers that we often look at and I check frequently in these patients are troponin and NT-proBNP. Now in more modern times, we often don't use Troponin T. We use something called high-sensitivity troponin, but this still can give us a guide. What we do know is if that troponin level is elevated, prognosis is worse. If the BNP is elevated, prognosis is worse. And if both are elevated, the prognosis is even worse. But again, this can allow us to get a sense and give a sense to our patients of what to expect in time.

Next slide. A newer safety system came out from the United Kingdom last year, and this was a study evaluating the use of eGFR and proBNP on mortality and shows that those 2 markers were also very prognostic. And that renal function and proBNP were elevated. That should portend a worsening prognosis as well.

One of the things you can really see is depending on those stages is the overall survival of these patients. And overall, we're talking about months. Prognosis for these patients is great. And when I meet them and go through these staging systems and tell them these things that this is a life-changing diagnosis.

Next slide. So I've told you that the mortality is very high for these patients. And initially, I will say, in medical school years ago, it was thought that amyloidosis was a Zebra. Something that was rare that you had to know and memorize for the Board, but not something that we would see commonly in practice. So okay, so the mortality is high, but it's a rare thing. Is that still true?

Next slide. So what I will tell you is, in the last few years, we've really learned that amyloidosis is not a zebra and is much more common than what we initially realized. There are 3 big studies that have shown this to us, #1 is an autopsy study, which shows that in 25% of patients greater than 80 years old, there was some level of TTR deposition in the myocardium. Out of those, 2/3 had left ventricular involvement, and there was significant cardiac involvement in

8% to 16% of people. So that -- if we think about our patient population, 8% to 16% of people greater than 80 probably have significant cardiac involvement.

There was another study looking at specifically the TAVR population, the less invasive treatment for aortic stenosis. Just 151 patients, but they did a PYP study on these patients, and 16% of them actually had evidence of true amyloid deposition through -- by the PYP. A very significant number for a procedure that is very common.

The third study is simply looking at the patient -- the inpatient population. Heart failure is a very common diagnosis on the inpatient side. Heart failure with preserved ejection fraction, if you just take that population and we did PYP studies on them, 13% of them actually had evidence of amyloid involvement. And again, not so rare and not a zebra.

Next slide. The top study is an international registry, where we try to understand the prevalence of patients that have amyloid. The THAOS data in the United States, about 50% of the patients with cardiac amyloid have wild type. Among the patients that have hereditary ATTR, there are 34 different mutations. About -- this is just again within the United States, about 45% of them are due to that valine to isoleucine mutation that we talked about in our initial patient case. And about 4% of the African-Americans actually have that mutation. The most commonly encountered subtypes of cardiac amyloidosis in elderly adults certainly is wild type followed by hereditary and followed by AL.

Next slide. So I told you that this disease is deadly and that it is actually not uncommon. How do we, in the medical field, recognize the signs and symptoms of the disease?

Next slide. So if amyloidosis then is challenging and this is exactly why the diagnosis is so challenging because there are so many different manifestations of the disease, particularly the way medicine is today, patients are often seeing many specialists, and there is not often 1 person who puts all of the pieces of the puzzle together, which is a big part of what I do in terms of education and why I'm here today. So certainly, there are CNS manifestations. We can see protenuria, we. See carpal tunnel syndrome, just as our patient had. Autonomic neuropathy in the form of orthostatic hypotension, the current urinary tract infection, all of these we see very frequently, glaucoma, papillary abnormalities in the eyes. GI manifestations very commonly I'm seeing nausea, vomiting, early satiety. Weight loss is extremely common and then this neuropathy.

In the cardiovascular side, we're often seeing that infiltrated cardiomyopathy, we see arhythmias, more often atrial arrhythmias, we see conduction blocks. When I teach cardiologists about this, I try to kind of hit home for red flag symptoms. If a patient that you see has heart failure, usually heart failure would preserve ejection fraction, and has any one of these red flag symptoms that should bring -- raise an index raiser -- index suspicion for amyloid: bilateral carpal tunnel, orthostatic hypotension or GI problems like constipation and diarrhea.

Next slide. The other reason that this disease is so challenging for cardiologists is that it very frequently can be misdiagnosed. That look that we saw in the initial echocardiogram was a thick wall, can often also be seeing hypertrophic cardiomyopathy. In the past, cardiologists have said, "Oh, well, but the pumping function of the heart is normal. This is just heart failure with preserved ejection fraction," and they don't often think further into the underlying reason. And again, a heightened index of suspicion if there is increased wall thickness of the myocardium without an obvious cause such as uncontrolled hypertension. There's that history of carpal tunnel syndrome, lumber spinal stenosis or spontaneous bicep tendon rupture. Heart failure, we can comment at right heart failure. Often, what we see is this increased wall thickness and the voltage on EKG is at normal or low. Low flow, low gradient aortic stenosis is something that we're realizing is often actually amyloidosis.

On cardiac MRI, as we mentioned, we see that the late gadolinium enhancement with the abnormal strain. We see natriuretic peptides, like BNP, that are out of proportion to how the patient presents, and we see persistently positive troponin. And a lot of amyloid patients will come to my clinic and have a diagnosis of myocardial infarction in the past because somebody knows that they had troponin elevated in the past. They didn't actually have an atrium coronary disease. It's that amyloid deposition in the myocardium that causes its release of troponin, which is a sign of cardiac damage.

Next slide. Again these disease symptoms are vague. Disease is not rare, and yet is deadly. So how do we, as cardiologist, diagnose this disease?

Next slide. So we talked a little bit about the EKG, but generally, the thing that was always taught and you would see a low QRS voltage. However, I will say the prevalence of this is very different, whether it's AL or TTR. I'm going to try to tell to physicians in training is that, "If you have a patient who has had signs and symptoms of amyloid and they have normal voltage on the EKG, that absolutely should not exclude the diagnosis of amyloid. If you have a patient that has all those signs and symptoms of amyloid and they have low voltage phase, you have another piece of the puzzle to that." We often also see poor R wave progression. We rarely see right bundle branch block or left bundle branch block.

Next slide. We mentioned the echocardiographic findings earlier, but just again, LV and RV wall thickening. We often see this classic bi-atrial enlargement where the atria which is supposed to be much smaller than the ventricle actually looks bigger. The atrial cavities look bigger than the ventricle. We see thickening of that intraatrial septum. We often

see pericardial effusion. We see diastolic disfunction, which can be very severe and actually show restrictive filling, and we can see the classic kind of sparkling myocardia.

Next slide. The next thing is something called speckle tracking. And this kind of -- this shows us different ways that the heart twists and conforms with each beat. It's not all about just squeezing. It's actually the torsion of the heart. And for reasons that we don't truly understand, there is a very specific look to the way that the heart twists with cardiac amyloids and what we see is a cherry on top. So basically, there can be strain, impairment in the entire myocardium except at the apex. For some reason that apex is preserved and the strain is normal. And that again should raise the suspicion that it's classic for cardiac amyloid. And to the point where we and the community are discussing, should we be doing strain on everybody, for instance, with aortic stenosis so that we're not missing these people.

Next slide. Cardiac MRI can be very helpful in changing the suspicion and then following responses to treatment we think. And again, what we expect to see is this diffuse subendocardial gadolinium enhancement, pericardial effusion, pleural effusion. We can get a sense that often the myocardium is very thick, the pumping function is preserved and the atria are big and dilated, and the LV and RV cavities are small, of course.

Next slide. There are a few different things on cardiac MRI that we're still learning, but what we do think can be helpful are a couple of different parameters. There's something called T1 mapping that we think can be very helpful to distinguish things like amyloid from hypertrophic cardiomyopathy. We can actually calculate and we call this extracellular volume. I like to think of it truly helping us quantify the amount of amyloid deposition that's in the heart, and I think it's something that we will be able to show and we can follow with response to treatment. Similarly, we can look at T2 mapping, which can show edema in the heart. You know that this is prognostic in AL, and what we need to understand is just how prognostic it's either with AL and TTR.

Next slide. There are a lot of questions to be answered. And we certainly don't know what is the best imaging modality to follow response to treatment. You don't truly understand what caused that late gadolinium enhancement in cardiac amyloid and the significance of it. Generally in the cardiac world, we think of late gadolinium enhancement as a sign of scar that can often lead to scary rhythms, like ventricular tachycardia. We're not seeing that with amyloid. It's something we still need to understand. I'm trying to understand if MRI can help us understand if those TTR fibrils are toxic. And again, we don't know which are the best parameters for following treatment. Is it the extracellular volume? Is that the T1? We are not sure, yet.

Next slide. So now we have a patient that we have a high suspicion of cardiac amyloidosis. How do we figure out the subtype?

Next slide. This is a diagnostic algorithm that we have at University of Chicago. It's very similar to a lot of published algorithms, and this is very cardiac-centered. There are neurologic algorithms as well from the approach of the neurologists, and we're working on creating an algorithm that would work for everybody. But in hours, when I would start with this, is that clinical suspicion, a lot of the things we talked about initially. So somebody who has heart failure with orthostatic hypotension and has a history of carpal tunnel. And at that point -- if at that point we think that the patient has amyloid, we've got to go to the next step, which would be ruling out AL amyloidosis.

Next slide. So the first thing we do to rule out AL amyloidosis is check that serum and urine protein electrophoresis and immunofixation, and we check serum free light chains. If any of those are abnormal, it leads to a discussion with hematology. If through that discussion, we need a biopsy, as we often do, we do often still end up doing a myocardial biopsy.

Next slide. If that initial work up, in terms of the electrophoresis, immunofixation and serum free light chain is negative, then we can think about a less invasive way of diagnosing. We can call it the PYP scan. Okay. What is the PYP?

Next slide. So the PYP is -- it can be different radiotracers. We use something called technetium. It can be done with DPD or PYP, but we think that that helps us see that the myocardium is -- has -- there is uptake in the myocardial when there is amyloid deposits in the heart. Tends to be particularly prominent in patients with TTR. So it's important to note that it can be seen uptick in the myocardium. It can be seen in people with AL amyloids, up to about 1/3 of patients with AL, which is why when we talk about that initial diagnostic algorithm, first step is to rule out AL with those initial lab work, but it can be helpful to distinguish.

Often where this is useful as well is in patients who are yet asymptomatic but they have a family history or genetic positive and we're trying to figure out at what point are they going to start showing cardiac symptoms. And we think that the PYP may actually be the first thing to be abnormal before we even see things on the cardiac MRI -- perhaps even before we see that rise in troponin and BNP.

Next slide. So the PYP can be -- there's a couple of different ways. There is a qualitative and a quantitative way of understanding. It is not a very challenging test. It does take some getting used to. And I think we're at the point that a lot of centers around the country are really starting to learn how to use this diagnostic test. The big thing for you to understand is that we talk about different gradations in terms of how much uptake there is in the myocardium. Grade 0

means that there is no uptake. And very likely TPR amyloid is not present. Grade 1 means that there is some uptake, and we're still trying to understand exactly what that means. Grade 2 is equal to rib, and Grade III is more. We know that Grade 2 and 3, there is a significant amount of amyloid deposit in the heart. Again, Grade 1, we're still trying to understand what that means.

Next slide. This is just to say that the ASNC did recently put out the practice points of how to use PYP, and I think these are now becoming more and more widespread, in terms of who we should be doing this test on and how to perform the test.

Next slide. We again to go back to our algorithm. If we order that PYP scan and we get a 0, meaning that there is no uptake in the myocardium, we tend to rethink our diagnosis. Is this truly amyloid? Or is this hypertrophic cardiomyopathy? Is this sarcoidosis? Let's rethink our diagnosis and go through the data, if we still are convinced, then we should do the biopsy. You're Grade 1. Now, this is the challenging part and, I think, should be institution-specific. Grade 1, again, we don't really know what to do. If your suspicion is high enough, probably proceed with a myocardial biopsy. Grade 2, there are many institutions who will not do a myocardial biopsy, or say, not confirm the diagnosis. Our institutions have changed, just in the past few years. Initially, the Grade 2s, we were still biopsying, and we were coming more and more comfortable with the PYP study. Now that we have become much more comfortable, the Grade 2s, we are not biopsying. And obviously, those patients have the diagnosis of TTR.

Grade 3 means, again, that there is more uptake in the heart than there is in the ribs. That is the diagnosis of TTR cardiac amyloidosis. And then we are left to understand is it wild-type or is it hereditary. The way we understand wild-type versus hereditary is purely with a genetic test. If the genetics are abnormal, that is hereditary, and at that point, we can perform genetic counseling.

Next slide. If the genetics are abnormal, then this is more likely wild-type TTR.

Next slide. The wild-type, as Eric mentioned, formally known as senile, it's nonhereditary. We expect that this generally affects the heart. It can cause carpal tunnel. It can certainly cause spinal stenosis. The neuropathy classically is uncommon, though, I say I see patients who complain a very similar symptoms with wild-type, tends to be much more male predominant, tends to be more caucasian predominant, tends to be in patients that are greater than 60. We don't truly understand why that happens. Is it a process of aging? Is it environmental factors that leads to that kind of initial (inaudible) to disintegrate than the (inaudible). We don't really understand.

Next slide. Now, again, then if there is -- if the genetics are abnormal, then this is hereditary TTR, and we need to think about genetic counseling.

Next slide, hereditary TTR, in the world, we know of over 100 mutations. The valine to isoleucine mutation, again, is the most common in the United States and is about 4% of African-Americans. And of the African-Americans who have amyloid, about 23% of them have amyloid leucine. [Val30Met] is more common world -- most common mutation worldwide. We often see neuropathy at the time of presentation. But the take-home point here is truly that the mutation can often dictate the phenotype. So things like valine isoleucine tend to be more cardiac phenotype, but that doesn't mean that they are only cardiac. There can certainly be a spectrum. There can certainly be neurologic manifestations depending on the different kind.

Next slide. So now that we know a patient who has amyloid and we know what type, where do we go from here? So hereditary TTR, certainly TTR in general, I think, really requires a multidisciplinary team. I'd like to think, as a cardiologist, I'm lucky to be a lot at the center of this and I can work with the hematologist to roll out AL amyloidosis. I can work with a neurologists when there are neurological manifestations of hereditary or wild-type. A genetic counselor here is very key for both pre- and post-test counseling. And as most of these patients have GI issues, a GI champion at each institution is certainly important as well.

Next slide. In terms -- we mentioned early on when I was an advanced heart failure cardiologist. In terms of what we can offer as an advanced heart failure cardiologists surely are LVAD, our heart pumps can rarely be done on these patients. The LV cavity is very small. These patients often have liver involvement, and it's a very, like, very rare that patients have an LV cavity that is large enough to support what's called the (inaudible) for an LVAD.

Similarly, for transplant, now with the advent of new therapies, we're really trying to understand the role of heart transplant. So certainly, where people that were meeting late in the stages of cardiac amyloidosis are candidates for heart transplant. It's somewhat still controversial in the cardiac community more with AL than with TTR. Initially, there were a lot of people that were doing liver transplant and heart transplants, and we've gone away from a lot of that at this point. And felt more that heart transplant alone was enough because it would take a long time for that liver to reinfiltrate a new heart. The challenge is that a lot of the patients after heart transplant can still develop neurological manifestations. Then a question will be whether or not things like our small interfering RNAs will help to treat post heart transplant patients.

Next slide. When I talk with my patients in clinic, given this life-changing diagnosis, and I talk about, okay, what are we going to do from here? How can we approach this disease? So certainly, we can stabilize the TTR tetramer. We can

talk about drugs like tafamidis or diflunisal. AG10 is a Phase III clinical trial with another stabilizer. You can talk about preventing the TTR production with drugs like patisiran and vutrisiran or inotersen. And then we can talk about the potential of breaking down the proteins with multiple antibiotic called doxycycline plus a vitamin called TUDCA. And this is how I tell the patients, and I am a strong believer in the ability to layer therapy. And I hope that we'll really see the combination of a small interfering in our RNA plus a stabilizer, perhaps plus something like doxycycline will really help our patients.

Next slide. Now in terms of who to treat? Certainly any symptomatic patient. If they had neurological pyramid. They've had heart failure requiring diuretic, they're hospitalized, they're short of breath, those we should treat. If they're symptomatic but they have PYP Grade 2 or 3 and have known mutation, those patients I would treat. The phenotype, again, can often dictate our treatment. Right now, FDA approval for cardiac is only with tafamidis. For patients who have mixed pictures, I am generally layering therapy with drugs like patisiran and tafamidis, inotersen and tafamidis and from the neurologic side, we are using patisiran and inotersen.

Next slide. So again, just to conclude, TTR cardiac amyloidosis is prevalent, deadly and underdiagnosed. We have new imaging techniques that allow for less invasive diagnostics. Therapeutic options are limited, but very hopeful new treatments exist.

Next Slide, and thanks a lot. That concludes my part.

Eric Green, Alnylam Pharmaceuticals, Inc. - VP and General Manager of TTR Program

Thank you so much, Dr. Sarswat. I really appreciate your taking the time today to share your experiences with us and with the audience. So we do have a couple of questions that have come in. We'll hold those to the end of the presentation. And I will again ask anybody in the audience, if you'd like, please go ahead and submit a question as we move over to pivot to our continued development of patisiran and vutrisiran in ATTR amyloidosis with cardiomyopathy. John?

John Vest, Alnylam Pharmaceuticals, Inc. - Executive Director of Clinical Research

Thank you, Eric, and hello to everyone joining us today. My name is John Vest, and I'm the Vice President of Clinical Research, overseeing all of our TTR programs. I'm very pleased for the opportunity to talk today in more depth about our development program in ATTR amyloidosis with cardiomyopathy.

We feel extremely well positioned to move forward with confidence in ATTR cardiomyopathy, is first and foremost, on our understanding of the pathophysiology of the disease and our ability to directly address the underlying cause of ATTR amyloidosis, by specifically reducing the pathogenic amyloid forming transthyretin protein. We've demonstrated this with patisiran and we are confident based on our Phase I observations with vutrisiran and modeling data that we can now achieve similar, if not greater reduction in transthyretin with vutrisiran and through quarterly or potentially less frequent subcutaneous dosing.

In addition to the marked improvement in neuropathy observed in hereditary ATTR patients on the APOLLO Phase III study, there is now encouraging evidence based on both exploratory data from the APOLLO study as well as subsequent data from global investigators suggest that TTR reduction has beneficial effects in hATTR cardiomyopathy, which we'll discuss in more detail in the coming slides.

Collectively, the sound therapeutic hypothesis, compelling pharmacodynamic effect, reducing the underlying cause of the disease and robust clinical observations provide a solid foundation on which we have designed our program with both patisiran and vutrisiran in ATTR amyloidosis with cardiomyopathy.

We have presented and published extensively over the years on the primary data from APOLLO, the pivotal Phase III study that was the basis of approval for ONPATTRO in hereditary ATTR amyloidosis with polyneuropathy. Importantly, that study included a spectrum of prespecified exploratory cardiac endpoints that were assessed in study participants with prespecified evidence of cardiac amyloid involvement referred to as the cardiac subpopulation.

Interestingly, while by design, the study enrolled patients with polyneuropathy, over half of the enrolled patients met criteria for the cardiac subpopulation, which we now know is reflective of the multisystemic natural history of this disease. The results of these cardiac data -- cardiac assessments were published in Circulation by Scott Solomon et al. What was most compelling about the data was the consistency across a variety of complementary assessments, which included an improvement compared to placebo and assessment of cardiac structure, evidenced by a decrease in LV wall thickness, cardiac function, evidenced by a decrease in longitudinal strain, a decrease in the important cardiac biomarker, NT-proBNP and an improvement in 10-meter walk test.

The Solomon et al publication also reports data supporting an acceptable safety profile for patisiran based on an in-depth analysis of cardiac events in both the overall study population and the cardiac subpopulation. Of course, the ultimate goal is to improve morbidity and mortality for these patients. So importantly, the significance of these

improvements in cardiac assessments was supported by a post-hoc analysis of safety data from the APOLLO study looking at the impact of patisiran treatment on mortality and hospitalizations across all patients in the study.

As shown on the left, you can see that for the composite of all-cause mortality and hospitalizations, we saw roughly a halving of those events -- event rates over the course of this 18-month randomized controlled study. It's important to note that these are exploratory in post-hoc analysis and thus need to be confirmed in ongoing trials. But you can start to see a consistency of findings across a wide spectrum of echocardiographic parameters, serum biomarkers, functional ability and outcomes that all support the hypothesis that we're pursuing in the ongoing APOLLO-B and HELIOS-B studies. We established the role of patisiran and vutrisiran in the treatment of patients with ATTR amyloidosis with cardiomyopathy.

In addition to these data from APOLLO, there were additional provocative findings that were presented by Julian Gillmore of the National Amyloidosis Center at the Royal Free Hospital in London. He originally presented data at the OTS meeting in Munich last summer. The data which were presented as an uncontrolled case series that includes patients who receive patisiran through an expanded access program further suggest a favorable effect of patisiran treatment on cardiac amyloid involvement. In the presentation, he showed serial technetium scintigraphy imaging from a representative patient. As mentioned in Dr. Sarswat presentation, technetium scintigraphy is an imaging modality that shows uptake of a radiotracer, in this case, DPD in the heart of a patient with ATTR amyloidosis. This image is from a 60-year-old man with a V30M mutation. He had a mixed phenotype, which includes polyneuropathy and cardiomyopathy. He's been on diflunisal but had continued progression of disease, and so patisiran was added. Shown here are images from baseline and then 12 months later.

In the baseline imaging, you can see clear uptake of technetium tracer in the heart with a signal intensity, which is the dark pixels substantially more intense than what is seen in the bone of ribs, which qualifies as Grade 3 uptake. And the subsequent image from the same patient obtained 12 months later, there's a marked decrease in cardiac uptake. You can see that the uptake in the heart is now equivalent to the uptake in the ribs. Accordingly, this would now be considered a Grade 1 or 2 uptake.

The clinical relevance of these findings will need to be corroborated in future studies. But it raises the intriguing possibility of regression of amyloid in the heart with RNAi therapeutics.

Importantly, these observations have now been further characterized with exciting data presented by Julian Gillmore, Marianna Fontana and colleagues this week during the European Society of Cardiology Meeting. The authors described these data from patients treated with patisiran and diflunisal as demonstrating "compelling evidence of substantial amyloid regression."

The data highlighted here are from 32 patients with hereditary ATTR cardiac amyloidosis. 16 patients received treatment with patisiran and 16 control subjects did not receive any disease modifying treatment. Patients were assessed with cardiac magnetic resonance imaging or CMR as well as echocardiogram, 6-minute walk test and the cardiac biomarker NT-proBNP at baseline and at 1 year. The very exciting findings from this study demonstrate that at 1 year, there was a substantial reduction in amyloid burden, which the authors characterized as "in keeping with amyloid regression" in 45% of the patients who received patisiran. Overall, the patisiran treated patients demonstrated a decrease in CMR assessment of cardiac extracellular volume, which is the compartment occupied by amyloid in this disease, as compared to an increase in extracellular volume in the control group.

The patisiran treated patients also demonstrated a substantial improvement in change in 6-minute walk test compared to the control group at 1 year. This is a very exciting finding for us, given that this is the primary endpoint of the ongoing APOLLO-B study and an important secondary endpoint in HELIOS-B.

The patisiran treated patients also demonstrated a substantial improvement in NT-proBNP compared to the control group at 1 year. No significant difference was observed in echocardiographic parameters at 1 year between patisiran treated patients in the control group.

As you can see -- as shown here, you can see that in the context of this data, we've continued to expand our robust development program in ATTR amyloidosis. On top of our ongoing work in ATTR amyloidosis with polyneuropathy, including the HELIOS-A study of vutrisiran that Eric outlined earlier, we now have 2 ongoing Phase III studies in ATTR amyloidosis with cardiomyopathy. APOLLO-B with patisiran and HELIOS-B with vutrisiran. I would like to now highlight these 2 cardiomyopathy studies in the coming slides.

We initiated the APOLLO-B study in late 2019. This is a study of 300 patients with ATTR amyloidosis, either wild type or hereditary, we have demonstrated evidence of cardiac involvement. Patients are required to have symptomatic heart failure, and they can be either TTR stabilizer naïve or beyond a TTR stabilizer at study entry. Patients are randomized one-to-one to patisiran or placebo, and the primary endpoint is the change versus baseline and 6-minute walk test in 12 months.

We selected 6-minute walk test as a validated surrogate endpoint in heart failure, and we identified this as an endpoint that will allow us to bring patisiran and the potential benefits of this therapy to this population as rapidly as possible.

We will, of course, look at a variety of secondary endpoints, including outcomes of death and hospitalization, as well as exploratory endpoints, such as cardiac biomarkers and cardiac imaging. The study is now well underway, and we are aiming to complete enrollment as rapidly as possible in 2021 and are encouraged by recent enrollment trends in this post-pandemic phase.

In addition to APOLLO-B, we are also very excited about HELIOS-B, which is our Phase III outcome study with vutrisiran in ATTR amyloidosis with cardiomyopathy. As outlined previously, vutrisiran is a subcu therapeutic that can be given with infrequent dosing at a low volume. We are confident that it will provide reduction in both variants and wild type TTR that's comparable, if not better, than that's seen with patisiran.

HELIOS-B is a 600-patient randomized controlled trial also in patients with hereditary or wild type ATTR. It's like APOLLO-B. All patients will have confirmed ATTR amyloidosis with cardiomyopathy at baseline and symptomatic heart failure. The study will include both patients on a TTR stabilizer baseline as well as TTR stabilizer naive patients. Patients will be randomized 1:1 to vutrisiran 25 milligrams quarterly or to placebo.

The primary endpoint is a composite of mortality and cardiovascular events to be read out, when the final patient reaches month 30, but we do expect to perform an interim analysis with the potential for an earlier data readout. There is also a robust package of secondary endpoints, including 6-minute walk test and the Kansas City cardiomyopathy questionnaire, a measure of quality of life that will allow us to fully elucidate the treatment effect of this therapy across a broad spectrum of disease manifestations. Enrollment in HELIOS-B is starting to reaccelerate after a slowdown due to COVID-19 in Q2.

I'll now highlight the global nature of our program in ATTR amyloidosis with cardiomyopathy. Across APOLLO-B and HELIOS-B, we will be activating over 100 sites in more than 40 countries. We believe this will allow for efficient enrollment of patients and yield a broad spectrum of patients on study, including both hereditary and wild type patients, patients with or without concomitant TTR stabilizer use of study entry in patients with a wide range of disease severity. With broad global reach will, therefore, ensure that these studies comprehensively elucidate the treatment effects of patisiran and vutrisiran on a widely representative global population and provide data covering monotherapy use as well as use concomitantly with the TTR stabilizer.

As with many clinical studies, enrollment did slow down considerably during the COVID-19 pandemic as patients were limited in their ability to travel and this hospital's limited treatment of non-COVID patients. We are pleased to see health care systems opening up around the world, and enrollment is accelerating in both of our studies.

Today, we are announcing the opportunity for a biannual dosing regimen with vutrisiran, which could further differentiate vutrisiran from other products currently approved or in development. In the left-hand panel of this slide, you see the robust and sustained TTR reduction data from our Phase I single-dose study of vutrisiran in healthy volunteers. It should be noted that we see TTR reduction of greater than 80% following single doses of 25 milligrams or greater.

In the right-hand panel of this slide, you can see pharmacodynamic modeling results, which illustrate the anticipated TTR reduction of multiple doses of vutrisiran. While we remain very confident in the 25 milligram once every 3 months dosing -- once every 3 month dosing regimen, which is currently being tested in HELIOS-A and HELIOS-B, we believe that the pharmacodynamic profile of vutrisiran also supports even less frequent dosing, such as a 50-milligram once every 6-month regimen.

Based on these modeled data, after repeat dosing, we expect to achieve 90% peak TTR reduction with either 25 milligrams every 3 months or 50 milligrams every 6 months. Indeed, vutrisiran administered with a regimen of 50 milligrams every 6 months is predicted to achieve TTR reduction that is similar to that achieved with patisiran at its clinical dose of 0.3 milligrams per kilogram every 3 weeks. And average TTR reduction of vutrisiran 50 milligrams every 6 months is anticipated to be comparable to what is achieved with 25 milligrams every 3 months at steady state.

Accordingly, we are seeking to advance this additional 50-milligram biannual dosing schedule for vutrisiran in order to further reduce the burden of current patients and the health care system and to provide additional optionality for patients and physicians.

Eric Green, Alnylam Pharmaceuticals, Inc. - VP and General Manager of TTR Program

Thank you, John. Very interesting new data from ESC this week and the potential for an even less frequent regimen for patisiran is very intriguing. Again, we have some questions coming in, but we're going to hold those through the end of the presentation. And now I'd like to transition to Rena to discuss the opportunity that we see with our overall TTR franchise. Rena?

Rena Denoncourt, Alnylam Pharmaceuticals, Inc. - Senior Director & Program Leader of Vutrisiran Program

Thank you, Eric, and hello, everyone. My name is Rena Denoncourt, and I'm the program leader for the vutrisiran program. As we turn to the ATTR franchise as a whole, I'll start by focusing on the substantial opportunity we see in hereditary ATTR amyloidosis within the existing ONPATTRO labeled indication.

Historically, disease awareness was low, patients were often misdiagnosed or undiagnosed and the unmet medical need was great. Through the introduction of ONPATTRO 2 years ago and Alnylam's commercialization efforts in the space, we've seen increasing disease awareness and diagnosis and, importantly, a steady increase in the number of hATTR amyloidosis patients with polyneuropathy on treatment.

From a franchise perspective, we are first establishing a strong foothold with ONPATTRO in this rare population. Next, assuming positive regulatory interactions following the HELIOS-A study, we will build on that foundation through the introduction of vutrisiran. Our aim is to increase the Alnylam market share in hATTR amyloidosis with polyneuropathy even further by providing multiple RNAi therapeutic options for patients.

Next, let's turn to a view of the full ATTR amyloidosis patient population and the significant market potential that exists here. Currently, there remains a significant unmet need in ATTR amyloidosis with cardiomyopathy. The overall size of the global population is significantly larger than the hereditary population as well. Again, assuming a positive study and positive regulatory interactions, APOLLO-B will provide a path to the additional 200,000 to 300,000 patients worldwide, through an expansion of the ONPATTRO label for the treatment of cardiomyopathy and ATTR amyloidosis patients. Thereafter, HELIOS-B will similarly do the same for vutrisiran, assuming clinical and regulatory success, thus providing the full ATTR amyloidosis population with 2 compelling treatment options.

The ATTR amyloidosis market is experiencing a time of significant evolution. Advances in the medical community have driven a deeper understanding of the disease itself, and there is now a greater awareness for how to care for patients in a multidisciplinary manner through centers of excellence, for example, as Dr. Sarswat referenced. The ability of treatment options and clinical trial availability site, the availability of treatment options and clinical trial opportunities have further bolstered physicians' motivation to identify the underlying cause of heart failure in their patients.

Importantly, we've also seen advances in technology and increased availability of diagnostic tools that can support accurate and timely diagnosis. Together, these trends drive significant potential for the next-generation of treatments as they are advanced.

Digging into the availability of these diagnostics a bit more, here we see data from Alnylam's no charge third-party genetic testing program, Alnylam Act. The program began in 2014 and has seen consistent growth over the past 7 years, with the number of physician accounts continuing to rise significantly each year. The number of tests conducted annually has also grown. Earlier in 2020, we did see that COVID-19 impacted the rate of testing, but we also see this rebounding more recently to approach pre-pandemic levels, as you see on the right.

Importantly, driven through strong disease awareness and educational efforts, the percentage of tests with positive mutations has remained steady even as the testing volume has increased dramatically over the years. Another important diagnostic advancement has been noninvasive and highly-specific cardiac scintigraphy imaging already discussed various times today. Claims data presented here illustrate a definitive increase in the number of technician PYP scans over the past 2 years in the U.S. Again, there was a drop in testing in Q2 2020 due to COVID-19, but we are already seeing the rate of testing nearly returned to pre-pandemic levels. The key point here is that physicians are now aware of ATTR amyloidosis. They appreciate the need to diagnose it. They have reliable tools available to do so, and they are actively utilizing these tools at a growing rate. Accurate and timely diagnosis is a critical component of driving positive patient impact. As more patients are diagnosed and diagnosed earlier, the size of the addressable patient population will grow. Additionally, as patients start treatment earlier in the course of their disease, they will gain greater benefit from that intervention and stay on treatment longer. Both dynamics work to drive the overall patient impact, which gives -- given all that I've just discussed, is anticipated to grow significantly over the coming years.

To maximize the potential for the greatest patient impact, Alnylam is actively building an integrated TTR franchise. Alnylam is committed to ATTR amyloidosis patients and the greater ATTR amyloidosis community. Through establishing this franchise approach, we can best ensure that patients will receive a treatment that meets their individual needs. We'll leverage and continue to build upon our well-established relationships with key opinion leaders in the space as well as the payers.

We will also continue to expand ONPATTRO globally and utilize that footprint as a springboard for vutrisiran. ONPATTRO will continue to be a highly attractive treatment option for patients while the introduction of vutrisiran is anticipated to provide the most compelling product profile of all current and emerging therapies.

The subcutaneous administration of vutrisiran and the infrequent dosing regimen will significantly reduce the treatment burden for patients and physicians, while maintaining the high bar for efficacy and safety that ONPATTRO, the first RNAi therapeutic has established in the field.

Here, you see how we will expand the value of the TTR franchise for years to come. The landmark APOLLO study supported the launch of ONPATTRO in 2018 and will continue to serve as the backbone of the franchise in the near term.

In the midterm, we will grow within the hATTR amyloidosis space with HELIOS-A and vutrisiran, while also expanding into ATTR amyloidosis with cardiomyopathy through APOLLO-B and patisiran. Finally, our long-term vision will come to fruition with the HELIOS-B data driving vutrisiran to market leadership across all ATTR amyloidosis.

Now I will conclude again by bringing our focus back to the patients we serve. They serve as a daily inspiration for all of our work and simply put, they are why we do what we do. Eric?

QUESTIONS AND ANSWERS

Answer – Eric Green: Thank you, Rena. Great sentiment and done. We do have some questions now, so we're going to move into more of the Q&A section. We have a few that's come in. So I'll start with one with Dr. Sarswat. But again, the audience has the ability to submit additional questions also.

So again, Dr. Sarswat, maybe a first question for you. What's been the experience you've been seeing in your practice with new patients being diagnosed over the last few years? Has it been steady? Are you seeing an increase? Is it more hereditary? Is it more wild type? I'd love to hear the dynamics there.

Answer – Nitasha Sarswat: Sure. So I think certainly, if you look at what happened somewhere around 2 years ago, things really changed in the whole field. And I felt that people became very excited about the disease, not just in cardiology but in neurology, and people are recognizing it and realizing that it's out there. But certainly, the volume really exploded about 2 years ago. And I think it's been fairly steadily increasing since that time. I would say there are just in our hospital, 2 new patients a week that are picked up. And it's interesting that those referrals, those people that are picking it up are more often than not physicians in treating because the training has even changed there where so much more of the disease, and they have that higher indexes suspicion going into the game. So absolutely, I think it has increased.

In terms of hereditary versus wild type, I think they're both being diagnosed at a faster rate. I think depending on where we practice, certainly, there's more hereditary or more wild type just based on the patient population around, but I think both of them are increasing at a very rapid rate.

Answer – Eric Green: And maybe that follows on to that question of index of suspicion. What do you think is the percentage of heart failure patients that are currently getting tested for -- by PYP or for TTR genetic testing of all heart failure patients, what do you think that percentage is right now? It's hard to estimate that number.

Answer – Nitasha Sarswat: Yes. I mean, still very low. I think that -- I mean, if you look at patients with systolic dysfunction, okay, very few, right? It's only the people that are it's -- I mean, I would say, 1 -- less than 1%. If you look at the heart failure with preserved ejection fraction population, I think that field, in general, is frustrating because we don't have the tools to offer that patient population. And it's frustrating for the patients, it's frustrating for us as the caregivers, so we're always searching for ways to help. And I think in the [HIPA] test population, we're recognizing and saying, hah, could this be more amyloid? And so I would say, out of those -- that particular population, maybe 5%. But I mean, certainly not as much as it should be. And I think that's also given for me on an academic institution, I don't think that's the practice in private practice.

Answer – Eric Green: Yes, that's fair. And maybe one question on the diagnostic algorithm you mentioned earlier and walked us through. There's a question, why is the PYP scan first instead of genetic testing for TTR mutation?

Answer – Nitasha Sarswat: Yes. I think that's really interesting. And a couple of people have brought that up. Truly, I think that there's some bias in that. If there are patients who do suspect and you initially send the genetic test that you may miss the other arm in terms of the AL, you may not -- you may be so focused. And there are patients that are carriers of the gene that don't actually express the true phenotype, right? So they could have AL amyloid and actually have a genetic abnormality, right? That's possible, particularly if they're an African-American, and they have their carrier of V122I. So that is part of the reason, just more in terms of cleanliness to not miss things. The other reason I think is not for genetic testing earlier on it, I think initially, we thought genetic testing was such a burdensome type of things of patients that, oh, you send it and you get it back like months later. No, it's just become so easy with things like the Alnylam Act that I don't think it's delaying time to treatment by pointing it later on. And again, to keep that algorithm clean. So we're not missing things and not treating people inappropriately.

Answer – Eric Green: That's great. Thank you. Maybe I'll switch over to John for a couple of questions. What do we have ongoing that will help us generate data with concomitant TTR stabilizer use? Given the mention you had of the data earlier today and the potential for the synergy, at least as that potential poster mentioned, what are we doing to generate those data currently, if anything?

Answer – John Vest: Yes. Thanks, Eric. It's a great question. Certainly something that is of great interest to us. And that was really part of the design of both APOLLO-B and HELIOS-B, we tried to highlight. We are allowing the baseline patients to come on to the study both who are on concomitant tafamidis as well as patients who are naive to stabilize their use. And when we take that and then combine that with the global footprint, of the study, as we highlighted in over 40 countries where we certainly believe that tafamidis use will vary greatly around the world. As we move through the studies, we would anticipate collecting robust data in both of those experiences that includes both concomitant use of stabilizers as well as monotherapy data.

Answer – Eric Green: That's great. And I guess related to that then, what are we doing to be able to find tafamidis naive patients around the world for these studies?

Answer – John Vest: Yes. Again, that's also a terrific question. And again, just to go back to that global footprint. That's -- we are working very closely with our CRO partners to really to scour the globe to make sure that we have a widely representative population. And again, it is certainly our anticipation that there will be many regions where it is either at a long time until tafamidis is available or potentially never available at all and/or with marked limitations and access. So we're -- we will be finding patients in those regions in order to make sure that we have that experience represented on the study.

Answer – Eric Green: That's great. Great. Maybe switching to Rena for a question for you and the overall portfolio. The question has come in is, do we have any plans to replace ONPATTRO with vutrisiran?

Answer – Rena Denoncourt: Thanks, Eric. It is a common question that we get. And certainly, we believe that many patients today are well served and will continue to be well served by ONPATTRO, and they'll want to stay on the product even when other options are available for them. So when we turn to newly diagnosed patients, we think that, that profile will be some patient population for which vutrisiran will be very compelling, and these patients will choose that option. But really, overall, the feeling is that the value of the franchise is that we can provide both of these options for patients and their physicians, and that allows them to choose which product works for them in their specific situation to meet their individual needs.

Answer – Eric Green: Thank you. Maybe back to Dr. Sarswat. You mentioned multiple specialties you work with for these patients, but how often are you working with those other specialties to manage your ATTR patients? And maybe any one specialty more often than the other?

Answer – Nitasha Sarswat: I would say, I mean, on a daily basis, we're talking. I think -- I mean, yes, on a daily basis. And I would say, hematology and neurology constantly, GI perhaps a little bit less frequently. Though, I mean, still -- I mean, I would say, once a week, but the hematologists and neurologists almost on a daily basis.

Answer – Eric Green: That's great. And I've heard of different ways that different institutions that do it. Are you physically all together daily or weekly? Or how do you guys just almost tactically manage that?

Answer – Nitasha Sarswat: Yes. We are not physically altogether. We try to schedule clinics on similar days so that it eases the burden on the patient so that they could, for instance, even neurologists in the morning and see me in the afternoon or something like that but that is a very challenging part. We meet at minimum monthly, weekly has been a little bit more challenging, but we needed a minimum monthly to review our protocols, our workflow, challenging cases and kind of just bounce things off of each other as well as research projects.

Answer – Eric Green: That's great. John, a question for you, I think. What are we thinking about for evaluating the biannual dosing for vutrisiran clinically?

Answer – John Vest: Eric, thank you. We plan on discussing the most appropriate strategy for advancing 50 milligrams every 6 months as an additional option for patients with regulatory authorities, and we'll communicate plans in the future as appropriate.

Answer – Eric Green: Okay. That makes sense. And questions that quite often we get about the HELIOS-B interim analysis, it says in the slide, it's an option. Are we willing to share anything else right now?

Answer – John Vest: Yes. Thanks, Eric. HELIOS-B is indeed designed with the option for an interim analysis. If we elect to execute that option, we will communicate details for the interim analysis at a future date.

Answer – Eric Green: Okay. That's good. Rena, question has come in, I think it will be best throw it to you. What do you see as the biggest competitor for the TTR franchise right now?

Answer – Rena Denoncourt: Thanks, Eric. That -- in our mind, that really comes down to the knowledge and awareness of the disease itself of ATTR amyloidosis. It's -- as I've talked through, it's gotten a lot better over the previous 2 years, the recent few years. But really, as is the case with most rare diseases, many of these patients are still undiagnosed and misdiagnosed and they're not getting the treatment that they need. So that really is the biggest hurdle that we're focusing on at this point to ensure the success of the franchise.

Answer – Eric Green: Excellent. Thank you. Maybe back to Dr. Sarswat, and I think you hit a little bit earlier, but I think it'd be interesting to really dive a little bit more. What do you see as the biggest barriers to getting to an earlier diagnosis of ATTR cardiomyopathy?

Answer – Nitasha Sarswat: I think it's exactly what Rena just said it, education. I think when you go to a cardiology conference at this point and there's a lot of hot talks about cardiac amyloid and it's coming there, but I don't think that it's come in full force and from what I gather to neurology and certainly to internal medicine. I think the primary care physicians are the gatekeepers and they're inundated with so many things on a daily basis with every -- each and every single patient they see. And they just need to have that indexes sufficient so know who to refer and how to get them in quickly. They need to be able to pick up the phone and say, I have this potential suspicious patient, what do I do next? And that's education. That's the biggest piece. I think a lot of that starts with trainees again. And as those trainees grow and get out into the workforce, as primary care physicians and as other specialties that will change too, but there's still a lot of work to be done in education.

Answer – Eric Green: Yes. That's a great point. And I think it's really interesting when you mentioned that physicians in training are actually the ones that are most likely to raise the flag and ask you to take a look at patients. So I think that's probably a very strong way to end. So that's most of the questions we have today. And I again, want to thank Dr. Sarswat for taking the time to share your perspective. I think it's a great set of slides, really interesting to hear you walk through and describe the experience you have every day in the clinic, as well as thanking John and Rena for everything.

And with that, I'll turn it back to Christine.

Answer – Christine Regan Lindenboom: Great. Thank you, Eric. So this concludes our RNAi roundtable for today. The replay and slides will be posted on Capella on our website later this afternoon with the transcript to follow shortly thereafter. Please do join us for our final RNAi roundtable of the 2020 series, which will focus on givosiran, and is slated to take place on September 14 at 1:30 p.m. Thank you, everyone, and have a great afternoon.
