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ALNY - 2017 RNAi Roundtable: Patisiran, in development for the treatment of hereditary ATTR amyloidosis

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PRESENTATION

Operator

Thank you, ladies and gentlemen, for joining today's RNAi Roundtable. (Operator Instructions) I would now like to turn the call over to Josh Brodsky for opening remarks. Josh, you may proceed.

Joshua Brodsky

Thank you, Michelle. Good morning, everyone. Thanks for joining us for today's RNAi Roundtable to discuss the progress we are making with patisiran in development for treatment of hereditary ATTR amyloidosis.

I'm Josh Brodsky, Associate Director of Investor Relations and Corporate Communications at Alynlam. With me today are: Eric Green, Vice President and General Manager, TTR Program at Alynlam; Jared Gollob, Vice President of Clinical Research; and Dr. Michael Polydefkis, Professor of Neurology at Johns Hopkins University School of Medicine.

Before I turn the call over to Eric, I just want to make a few comments. Today's RNAi Roundtable is the first in a series of roundtables that we are hosting this summer and early fall. Today's event will end at around 11:45 a.m. Eastern Time. Eric will moderate a Q&A session at the conclusion of the presentation. (Operator Instructions) And finally, as a reminder, we will be making forward-looking statements. And we encourage you to read our most recent SEC filings for a more complete discussion of risk factors.

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

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

Thank you, Josh. Good morning, and thanks, everyone, for joining us today to hear little bit more about our TTR programs.

So starting on Slide 6. As you all know, Alynlam is the industry leader in RNAi therapeutics, which represents a whole new class of innovative medicines. RNAi is a powerful approach for gene silencing that harnesses a natural and catalytic mechanism. And through Alynlam's efforts, RNAi is now a clinically proven approach.

On the next slide, we can see our current clinical development pipeline. We have developed a broad number of products that are targeting different liver-expressed proteins. And we have demonstrated human proof-of-concept with 7 different products, including 4 programs that are in the late stage of the development. You can see today, obviously we will focus on our TTR programs with most of our time actually spent on patisiran. And Dr. Gollob in a few minutes will also provide a brief update on ALN-TTRsc02.

As a reminder, patisiran is the furthest along in the development path in our pipeline, having completed an enrollment in the APOLLO Phase III study in early 2016 and excitingly top line results expected in the next few months. We have been generating and sharing data from the Phase II

open-label extension study, or OLE, for a while now. Patients that completed dosing on that study as well as patients that completed APOLLO are eligible to roll over to the APOLLO OLE study for long-term treatment with patisiran. In addition, we have opened an expanded access protocol here in the U.S..

On the right side of the slide, you see the ALN-TTRsc02, which is currently in a Phase I study in healthy volunteers. This product utilizes our ESC, or enhanced stabilization chemistry. And preliminary data suggests the clamped knockdown of TTR production that will allow for a low volume quarterly subcutaneous dosing. We believe this could be a best-in-class product profile in the future.

As you saw from the agenda, Dr. Michael Polydefkis from Johns Hopkins University School of Medicine will discuss the path to a diagnosis, including a few recent cases he has had. After Dr. Polydefkis speaks, Dr. Jared Gollob, from Alnylam and the lead position on our TTR Program, will discuss some of the endpoints in APOLLO as we get ready to see the results from that study as well as some highlights from our final Phase II OLE data that were presented earlier this year.

And finally, at the end of the segment, I will discuss our preparations for commercialization of patisiran. As Josh said, we will have a Q&A session at the end of all the presentations, so please remember to submit your questions throughout the presentations for any of the speakers, and we will get to those at the end.

With that, I would like to welcome Dr. Polydefkis. Michael?

Michael Polydefkis

Thank you. So I'll start on Slide 7. And the hallmark of hATTR is deposition of amyloid. But underlying that is over 120 defined mutations or genetic variants. And this slide shows a number of those different variants. On the right are variants that have a predominantly cardiac phenotype presentation. On the left are genetic variants with more of a neurological phenotype.

And on the next slide, it's not surprising that underlying this genetic diversity, patient will have a variety of complaints at diagnosis. The most common will be sensory numbness or sensory loss or muscle weakness. But other symptoms are also present, such as difficulty with urination, GI complaints, dizziness or abnormalities on cardiac testing.

The next side, Slide 13. It's easy to imagine how these different symptoms can cause patients to see a variety of different medical specialists. So this confusing slide can depict the odyssey that patients go through to reach a diagnosis. So it's not uncommon. In fact, it's probably the rule where patients will see many physicians. They could start with their primary care physician, go to a gastroenterologist and they'll put an incorrect diagnosis, to a urologist, a neurologist, a geneticist, and then arrive at a correct diagnosis. And this pathway can take years, commonly 4 to 5 years to reach a diagnosis.

As physicians, we have a number of tools at our disposal. And Slide 14 depicts these tools. So clearly, patient symptoms or their signs of examination provide us clues to the diagnosis. But early on, this could be quite nonspecific. If a patient comes to us with a history of amyloid or an aggressive neuropathy, that could be a clue. But that's often not the case. Genetic testing can identify patients at risk for developing the disease. Diagnostic tests, such as echocardiograms, nerve conduction, can demonstrate a symptomatic involvement. But typically, it's the pathology that's viewed as the gold standard to nail down a diagnosis.

On the next slide, Slide 15, there have been a number of attempts to try and identify red flag symptoms or clusters of symptoms that could alert physicians to the diagnosis. So a patient with a progressive sensorimotor polyneuropathy combined with something else, such as a family history, early autonomic dysfunction, GI complaints, unexplained weight loss, cardiac abnormalities, renal abnormalities or ocular abnormalities, all clearly (inaudible) for this diagnosis. But it is rare and then very often is missed early on.

Similarly, on the next slide, Slide 16, a patient presenting with right-sided heart failure or hypotension and someone who previously has hypertension, combined with other features, such as family history, decreasing QRS voltage, a characteristic speckled pattern on echocardiogram, enhancement

by cardiac MRI, heart failure with preserved ejection fraction, the presence of a sensory autonomic neuropathy or carpal tunnel syndrome, all again increase the diagnostic yield.

So we thought it would be helpful to view some typical cases. These are all recent cases I've seen in the past few months. So the first case, which might be labeled as serendipitous diagnosis with a 74-year-old woman without a significant past history, 4 years ago, she presented to a GI physician with a complaint of diarrhea. To that physician's credit, they noticed a murmur, referred her to a cardiologist. And a subsequent workup included an echocardiogram, which had this characteristic speckled pattern for amyloid. Her fat pad biopsy was positive. A genetic testing revealed the T60a variant. So a person without a known family history had a new diagnosis, amyloid cardiomyopathy.

She made the comment, "I stopped seeing patients at that point because they have nothing much to offer." And when she saw me last week, she was interested in these emerging treatments that she's been hearing about. At that time, she has well controlled Class II heart failure and she has significant neuropathy that was her most limiting feature of her disease with a Neuropathy Impairment Score of 42.

The next case was another new diagnosis of amyloid. This was a 63-year-old man, who was quite vigorous. He enjoyed excellent health up until about 3 years earlier, when he developed knee pain that caused him to stopped refereeing hockey games. He underwent total knee replacement but was not recovering as expected. About 2 years before I saw him, he had a foot infection that required IV antibiotics. He ultimately had an amputation. And he commented that, that was when he first noticed numbness to this feet and shortly thereafter his hands. So one wonders if that numbness did contribute to his infection or ultimate amputation.

And then a year later, he developed difficulty with fine motor tasks, buttoning his shirt. He had a lift installed in his house to help get up the stairs. He saw a neurologist, who diagnosed an advanced sensorimotor neuropathy. And it then came out that, in fact, his father had, had a similar progressive decline about a decade earlier. His father quickly was spent out, spent the last few years of life in a nursing home and died about 8 years after symptom onset. So that history prompted a late possibility of an amyloid diagnosis. A (inaudible) nerve biopsy was performed last month. It was positive for amyloid. Genetic testing revealed the most common mutation, V30M. And this patient, to give you a sense, has quite advanced neuropathy with a NIS score of 101.

The last case highlights some evolving diagnostic tools on Slide 19. This was a 59-year-old athletic, former Division I athlete, who 2 years before I saw him noted he had difficulty keeping up with family members on trips to the zoo. A few months later, his primary care physician noticed some mild foot drop. A few months later, he had difficulty hiking, the thing that he had previously been quite good at and difficulty of biking to work. The evaluation was quite thorough but was unrevealing with the exception of a glycated hemoglobin that was elevated at 6.5%. And he was given a diagnosis of the diabetic polyneuropathy. And that's how he presented to me. On further questioning, he reported a history of erectile dysfunction and a tendency towards constipation that was new. But neither complaints with things he offered were prominent for him. His workup revealed, similar to the other patients, a significant neuropathy and NIS score of 84 and marked abnormalities under conduction.

On the next slide, Slide 20. We did a skin biopsy. And on the left, panel A is notable for the absence of epidermal nerve fibers, so significant small fiber neuropathy. And panel B, there are very few fibers in sweat glands as shown by the arrows.

Next slide, we stain the skin with (inaudible) red. And we saw a characteristic (inaudible) staining in the deep dermis by panel B. And that area was (inaudible) by panel B1. Panel E shows the rest of (inaudible)

The next slide, ironically, the patient was getting his nerve biopsy at the time he does the skin biopsy. But the nerve biopsy in panel A confirms that the cause of red staining at panel A1 (inaudible) caused the red staining.

The next slide, Slide 23. (inaudible) testing that demonstrates the (inaudible) variant. And again, this was the de novo (inaudible) a patient without a known history for familial amyloidotic.

Next slide. This was the first case at a hospital diagnosed by skin biopsy that demonstrates the evolving (inaudible) represented how hATTR can be variable.

(inaudible) and little complaints (inaudible) often hallmarks of the disease.

So final slide. (inaudible) represents how hATTR can be heterogenous (inaudible). It could be men, women (inaudible)

So that image of a sunrise, I think, reflects my opinion that this the dawn of a new era. (inaudible) but now (inaudible) and I think an exciting development. Thank you.

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

Excellent. Thank you, Dr. Polydefkis. I always appreciate the opportunity to be reminded about what the patients with this disease would go through just even to get a diagnosis. So your cases, I think, were very illustrative, very interesting.

I'd now like to turn the call over to Dr. Jared Gollob.

Jared A. Gollob - *Alnylam Pharmaceuticals, Inc. - VP of Clinical Research*

Great. Thank you, Eric, and good morning, everybody. So we're on Slide 27 now. And so Slide 27 really is highlighting that ATTR amyloidosis is a multi-systemic disease, a disease with multiple, different clinical manifestations. The main manifestations result from the polyneuropathy due to amyloid deposition in the nerves and the cardiomyopathy due to amyloid deposition in the heart.

The systemic manifestations of the disease are largely due to liver-derived amyloid, TTR amyloid. The polyneuropathy involves both sensory, motor and autonomic nerves. The sensorimotor neuropathy can result in neuropathic pain, loss of sensation, muscle weakness, which then results in inability to walk and inability to use one's hands. But the autonomic neuropathy can also be very disabling and can result in orthostatic hypotension, which is low blood pressure, sexual dysfunction, recurrent urinary tract infections and importantly also gastrointestinal manifestations, another big problem resulting from the autonomic neuropathy that can in turn lead to weight loss and malnutrition.

So essentially, all of these manifestations come from liver-derived TTR and are large due to the disease affecting the nerves and the heart. So the cardiac manifestations include things such as conduction block, which can also be a result of the autonomic neuropathy as well as cardiomyopathy leading to heart failure.

On Slide 28, this is a slide similar to the one that Dr. Polydefkis just showed earlier. As he mentioned, there are more than 120 different mutations causing this disease. And mutation and the geographic origin of the patient with a given mutation can influence how the patient presents, whether they present predominately with neurologic manifestations or predominantly with cardiac manifestations. But what's important is regardless of how the patient presents, ultimately a majority of patients will manifest both neuropathy as well as cardiomyopathy, the so-called mixed phenotype.

Moving to Slide 29. This brings us really to a look at the historical nomenclature for hATTR amyloidosis. And historically, the disease has been described based on how patients present. Patients presenting predominately with neuropathy were called familial amyloidotic polyneuropathy or FAP. Patients presenting predominantly with cardiomyopathy were known as familial amyloidotic cardiomyopathy. But as just mentioned, most of these patients will progress to the point where they have both neuropathic and cardiac manifestations. And therefore, the lexicon has evolved to the point now where the disease really is referred to as hereditary ATTR amyloidosis, acknowledging that the disease often has both neurologic as well as cardiac manifestation.

Slide 30 has some illustrations of what the neuropathy can do to patients and how it can manifest. So the loss of sensation can lead patients to developing thermal burns on their feet and on their hands. And that's shown in the left panel. The involvement of motor nerves can lead to loss of motor nerves and motor axons, which results both in muscle weakness, motor weakness and also actual wasting of the muscles shown here with profound wasting of the muscles in the hands and in the feet and the distal leg. The loss of sensation and weakness can cause profound damage to the joints in the legs, especially in the knees and in the ankles and the feet. And in the bottom right, in Portugal, the disease is known

as the mal dos pezinhos or the disease of the little feet because you can see the deformities resulting from severe joint damage in these patients with advanced sensorimotor neuropathy.

Slide 31 provides a summary of the so-called Neuropathy Impairment Scores, NIS, and how these has evolved over time. So Neuropathy Impairment Scores are a way to measure and follow the neuropathy or the polyneuropathy in patients with neuropathy, not just patients with hATTR amyloidosis. And in fact, the early neuropathy scores, such as NIS-LL and NIS, were initially developed for patients with diabetic polyneuropathy. But over time, this composite score has evolved to develop and include the so-called plus 7 components, which includes neurophysiologic testing as well as inclusive eventually of test of autonomic function, which brings us to the modified NIS+7 score, which has different variations.

Shown here is a modified NIS+7 that is used in the Alnylam APOLLO study as well as a variation on that, the modified NIS+7 used in the IONIS Phase III study. The modified NIS+7 score includes the motor strength and reflex examination based on just the regular neurologic exam but also includes the addition of quantitative sensory testing, nerve conduction studies that actually focus on axonal loss, which is the hallmark of this particular type of amyloidosis and also includes autonomic measures, such as postural blood pressure. The IONIS score also retains the sensation component of the NIS. The quantitative sensory testing is thought to be superior in that it is a machine-driven analysis of sensation, heat pressure -- touch pressure and heat pain, covering a larger portion of the body surface area.

If we move now to Slide 32, whereas the Neuropathy Impairment Score can assess the polyneuropathy, it's important also to have other additional assessments that could fully factor how the polyneuropathy actually affects patients and allows us, therefore, to determine how a particular intervention can provide clinical benefit to a patient. So in addition to looking at neuropathy -- neurologic impairments through the modified NIS+7, we can also look at motor function and look at how well a patient can walk using a 10-meter walk test, how well they can use their hands by measuring grip strength. We can measure how well they can walk by looking at their FAP stage or their polyneuropathy disability score, which is a measure of whether they need walking assistance. We can measure autonomic symptoms using the COMPASS-31 scale. And we can also measure patient's nutritional status using the modified body mass index.

We also have novel measures, such as Dr. Polydefkis described, we can look at the disease (inaudible) and look at nerve fiber density in the skin and amyloid burden in the skin. And of course, we can also look at changes in the heart with echocardiogram and cardiac biomarkers. These various measures ultimately culminate in how the disease affects quality of life and physical functioning and using scores, such as the Norfolk Quality of Life to look at quality of life and physical functioning as well as being able to measure activity and social functioning or the level of disability that a patient has using the so-called R-ODS or the Rasch modified overall disability scale.

Moving on to Slide 33. This is just to highlight what the Norfolk Quality of Life questionnaire is comprised of. This was initially developed for diabetic polyneuropathy but was then adapted and evolved for the use specifically in patients with hereditary ATTR amyloidosis with polyneuropathy. There are 5 different domains that measure daily living, physical functioning and large and small nerve fiber function, autonomic neuropathy as well as symptoms. The higher the score, the more your impairment of quality of life. And what you could see at the bottom of this slide is that as the disease stage advances, the quality of life gets worse, meaning the Norfolk Quality of Life score goes higher. And we can even see that across the different domains of the score. As the stage increases, the score across the different domains also increases, showing impairment of quality of life with advanced disease state.

Slide 34 provides a summary of the Rasch-built Overall Disability Scale. And this is a 24-item patient-reported outcome instrument that measures really activities of daily living, how well a patient can wash dishes, fasten buttons, move a chair, walk, bathes himself, read the newspaper. And these are very important in really assessing the level of disability caused by the disease.

On Slide 35, we come to the patisiran Phase II open-label extension study, where we were able to look not just the safety but also applied many of these clinical endpoints for the first time in this disease to see how they would perform in this disease. The Phase II open-label extension study was a 3-year study that was recently completed. And this slide shows the various measures that were performed on the study, which included mNIS+7 as well as various clinical measures, such as quality of life, modified body mass index, autonomic symptoms but also included skin biopsies to look at nerve fiber density in amyloid burden and also included cardiac disease measure.

Slide 36 shows the safety profile for patisiran over 2 years. And patisiran was found to be generally safe and most tolerated over a 2-year period of time with patients getting a dose of drug once every 3 weeks. So note here that there were no study drug-related serious adverse events. And most of the adverse events that we saw were mild or moderate. The most common adverse event were still relatively infrequent. And these were infusion-related reaction in about 20% of patients and flushing, all of which were mild. And importantly, there were no clinically significant changes in liver function tests or renal function or hematologic parameters, including platelets, where we saw no significant changes in platelet count in patients that were treated with patisiran over this 2-year period.

Slide 37 presents the mNIS+7 date that we have presented elsewhere recently. And looking at this waterfall (inaudible), what you can see here on the left panel is that the majority of patients, 74% of patients showed a decrease in their mNIS+7 at 24 months compared to baseline, which represents an improvement in their neuropathy or an improvement in their degree of neurologic impairments. On the right, you can see that for the whole group getting patisiran, there was a minus 7 point change or a reduction or improvement in neuropathy in patients getting patisiran, which compared historically to the expected or anticipated 26 to 30 point increase or worsening of neuropathy seen in natural history studies and in the placebo arm of the Phase III (inaudible) trial. Other parameters, clinical endpoints that were looked at, including the EQ-5D quality of life, the R-ODS as mentioned and cardiac measures, all showed remarkable stability over that 2-year period of time.

The next 2 slides presents some of the exciting skin biopsy data that Dr. Polydefkis was referring to earlier. These samples -- skin biopsy samples were analyzed in Dr. Polydefkis' lab in a blinded manner. So the operators are blinded to patients and to time points. And we noticed that amyloid could be detected in 80% of skin biopsies at baseline, highlighting the sensitivity of this specific diagnostic test. But what was noted here and what you can see on the bottom left panel in the figure and at the table to the right, that when we look at the change in dermal amyloid burdens over time, you can see that even starting at 6 months after the start of treatment, there's a significant decrease in the dermal amyloid burden both in the distal thigh and the distal leg. And that decrease is maintained out for 24 months of treatment. And we can see the numbers behind those changes on the table on the right. And then in the figure on the far right, what you see visually, the dermal amyloid burden going down over time. The top panel of baseline shows the red staining amyloid in the dermis at baseline. And then it shows smaller amounts of amyloids at 24 months in the patients treated with patisiran.

Slide 39 shows the corresponding results for sweat gland nerve fiber density. And what you can see here is an inverse correlation with sweat gland nerve fiber density and amyloid burden. So starting at 6 months and persisting out to 24 months, we see an increase in sweat gland nerve fiber density in the distal thigh and distal leg representing nerve fiber regeneration, which again inversely correlates with the decrease in amyloid burden that was seen in the skin. And the panel on the right dramatically shows visually the green staining within the blue-colored sweat gland shows the nerve fibers. So you can see (inaudible) of nerve fibers at baseline. And then at 24 months, you can see much more of the green staining, which shows the regeneration of these nerve fibers. We also looked at intraepidermal nerve fibers, which remained stable over that 2-year period of time.

So moving on to Slide 40. So having reviewed those very encouraging results from the completed Phase II open-label extension study, I want to turn now to a review of the ongoing Phase III APOLLO study and its companion open-label extension study. We're excited that the Phase III study is nearing completion. And as Eric mentioned at the outset, we will be presenting top line results in the coming 2 months.

Just as a reminder, this study has 225 patients. So this was the largest study to date in patients with hereditary ATTR amyloidosis with polyneuropathy. And it accrued a wide variety of patients with a range of disease severity mutations. Patients were randomized 2:1 to patisiran once every 3 weeks or to placebo for 18 months. And the endpoint shown here are essentially the same endpoints that I just showed and reviewed for the Phase II open-label extension study. But the one difference being that it also includes the Norfolk Quality of Life as the first secondary endpoint. But you can see the other secondary endpoints here that are looking at disability, the R-ODS, looking at the ability to walk, 10-meter walk test, looking at some autonomic symptoms, COMPASS-31 and a number of exploratory endpoints, such as skin biopsy measures. These are all unique to the APOLLO study and are not included in the inotersen PCR study.

Moving on to Slide 41. As a reminder, Ionis reported their top line neuro PCR Phase III results several months ago. And it was significant in that it did show a statistically significant benefit observed for the co-primary endpoint of mNIS+7 and Norfolk Quality of Life at 15 months. They also saw statistically significant differences for both of those endpoints at 8 months. And they noticed that the benefit was seen regardless of TTR mutation and also regardless of the disease state. And That was very encouraging. It really validates what we saw in the Phase II open-label extension study and gives us confidence on what we expect to see in the APOLLO Phase III study.

However, it should be noted that on the IONIS study, the top line results did point out some key safety findings, which included thrombocytopenia and renal serious adverse events. 3 patients had thrombocytopenia serious adverse events, including 1 patient who died due to intracranial hemorrhage. 4 patients actually discontinued treatment due to renal toxicity, including 2 who had renal serious adverse events. And these platelet and renal adverse events led to the implementation of enhanced monitoring. And Ionis anticipates that regulators will require safety monitoring in the prescribing information, if approved. So the details of that safety data, the review still ongoing. And we expect to see further results from the inotersen study probably later this year. But again, to note here, the efficacy data we're encouraging with regards to APOLLO. But the safety findings here with this (inaudible) did have some findings that were of concern and that will be further evaluated in the near future.

Finally, given we're obviously very excited about patisiran and the upcoming APOLLO readout, we also wanted to note that ALN-TTRsc02 presents another opportunity within this space to have the potential for the best-in-class drug. TTRsc02, as Eric pointed out earlier, is a ESC-GalNAc-conjugate. And we have an ongoing study in normal healthy volunteers, where we see remarkable clinical activity. After just a single 50-milligram dose, we've noticed a knockdown at day 90, so 3 months after that single dose of greater than 80% with maximum knockdown of 97%.

This, by far, is our most potent Alynlam RNAi therapeutic to date. And with this sort of potency, we anticipate quarterly dosing. So if we compare this to inotersen or even to revusiran, which was our weekly first-generation conjugate that was now discontinued, that would require 52 doses per year, will be the equivalent of 4 doses of ALN-TTRsc02. And as shown on this slide, fortunately the safety profile has been quite benign so far. And as shown here, it's been generally well tolerated in healthy volunteers.

And then finally Slide 43 just further shows the TTR knockdown data looking at the various dose groups across the study. The 50-milligram dose is shown in the very light blue triangle. And you can see that the knockdown of TTR is fairly rapid even after a single dose. And one can see this remarkable persistence of the TTR lowering effect going out not just to 90 days, but even out as far as 180 days and beyond. Again, this after just a single dose, which gives us confidence that we can dose this type drug, TTRsc02 at least quarterly and be very effective potentially in these patients who have ATTR amyloidosis. So we're very excited about TTRsc02. We're just still in early stages of development but could provide an exciting option for patients with less frequent dosing and also a lower dose.

Finally, in summary, on Slide 44, we've shown that this disease is a multi-systemic disease with multiple different clinical manifestations of polyneuropathy, that are often accompanied by cardiac involvement, which could lead to progressive disability, diminished quality of life and death. These composite Neuropathy Impairment Scores like mNIS+7 along with additional clinical and biomarker endpoints have the potential to demonstrate the clinical benefits of these novel therapeutics what this would be. The open-label extension study data with patisiran suggests that TTR lowering does have the potential to have a disease-modifying effect on the polyneuropathy in ATTR amyloidosis as shown by the effect on mNIS+7, dermal amyloid burden and sweat gland nerve fiber density. And the emerging results of the randomized Phase III trials with patisiran and inotersen will further elucidate the utility of these endpoints and other endpoints in assessing the magnitude as well as the clinical meaningfulness of the response to treatments.

And in addition, ALN-TTRsc02 offers the potential of a best-in-class profile with a quarterly low-volume dosing with clamp to knock down of TTR.

So I will end there and I will turn it back over to Eric.

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

Great. Thank you, Jared. And I just want to note on the previous slide with those data from the ALN-TTRsc02 was actually new data and an update from what we presented back in December at the R&D Day. So this is showing continued durable knockdown of the TTR for quite some time. So quite exciting.

Okay. And moving on to Slide 46, and the rest of the segments here. Let's now discuss our -- the commercial opportunity in ATTR amyloidosis and in addition some of our preparations to commercialize patisiran.

So on 46, we can see here some key milestones that we've been working towards in targeting for our patisiran program. APOLLO data as we've said has been mid-2017. And as we define that, it's Q2 to Q3, so we can then further clarify that, that's likely mid-to-late September when we see the top line results from that study.

Assuming positive data from that study, as we heard from Jared reasons to be encouraged that would be true, we expect to file the NDA here in the U.S. by the end of the year, 2017, and file the marketing authorization application in Europe shortly thereafter. Therefore, assuming positive approvals from the regulatory agencies, we would be preparing to launch patisiran, both in the U.S. and Europe in 2018.

On Slide 47. As a reminder, our Alnylam will solely commercialize patisiran in the U.S., Canada and Western Europe, those countries that are highlighted in blue on the slide here. And in the rest of the world, we will be working with Sanofi-Genzyme and will receive royalties on sales in their territory. We have established our European business with a headquarters in Zug, Switzerland and continue to build a robust development group in the U.K. at our Maidenhead site also.

On the next slide, as a reminder, there are no approved drugs for the treatment of ATTR amyloidosis here in the U.S., however, in Europe, with tafamidis from Pfizer has been approved for the treatment of FAP Stage 1 patients. Though there have been numerous studies that have been published that show that many patients progress even as they're being treated with tafamidis. And one example you can see here in the table on the right of the slide in (inaudible) .

In addition, orthotopic liver transplant has been a treatment option for some patients, though the numbers of transplants have been declining. And with better outcomes occurring primarily in younger patients and in particularly younger patients with the V30Met mutation. There are some other investigational therapies in clinical development, as we mentioned, obviously, patisiran and inotersen are 2 that are at the forefront in late stage development.

On the next slide similar graphic as we've shown. Again, we see these as a spectrum of disease. ATTR amyloidosis is an ultra-rare genetic disease with an estimated global prevalent of approximately 50,000 patients. Common estimates count about 10,000 patients with predominant polyneuropathy signs and symptoms. However, some more recent data sets have suggested that anywhere from 20% to 30% or perhaps more of patients actually have a mixed phenotype, that is both with polyneuropathy and cardiomyopathy symptoms as Jared had just mentioned.

And due to the (inaudible) dominant nature of the disease, that is how the disease mutation is transmitted within families, we actually see some endemic areas around the world such as in Portugal, Sweden and Japan. So to put it more blankly -- bluntly, patients are not uniformly distributed around the world, and that makes it a little bit more challenging to find a diagnosis [type] . As we've hopefully shown already in Jared's presentation for patisiran, we feel we have the potential to address some of these unmet medical needs in this disease area.

On Slide 50 is a framework that shows that success in rare disease is -- often follows a certain path. We feel a lot of these principles will apply to hATTR amyloidosis. By definition, rare diseases are not common and patients can be hidden amongst people with more common diseases. Thus, disease education and awareness of the disease itself are critical before a physician can even consider this disease as a diagnosis. To determine the best course of treatment though, the correct diagnosis must be made. As we heard earlier, patients can remain undiagnosed or in some cases worse, misdiagnosed for years. Patients must ultimately have access to therapies and we, at Alnylam, will be working on that with payers and governments around the world as appropriate. And given the small patient population and increasingly competitive market, success also requires probably a best or first-in-class product profile. Markets are simply too small to share dramatic amounts of market share as we don't need to. We feel this is best for patients.

Given the chronic nature of this disease, we feel that integrated support services can also be helpful to patients and their caregivers, not only as they initiate treatment but potentially for the years to come, as they continue to receive that treatment. An engagement with patient advocacy groups is essential as they are powerful and an important voice for patients with rare diseases.

On the next few slides, I will walk through a couple of these in a little bit more detail. On Slide 51, we'll see that we have recently launched 2 new websites focused on disease education. The one on the left is aimed for health care professionals and helps bring up the point of view that it is a such a multi-systemic disease and is a bit of a puzzle to try to solve to get to the proper diagnosis. The one on the right is aimed more for patients

and their families and is focused on education, understanding the disease and then eventually be able to talk to not only your physician about the disease as well as potentially family members, given how this is transmitted through families.

On Slide 52, education also happens at a personal level, not just the -- in person through digital or website. And today, we've had over 4,000 different tier engagements between Alnylam and physicians and other health care professionals at conferences and smaller visits over the last several years. We expect this number actually to accelerate in the coming years as our organization grows, and assuming approval, we are able to talk about and educate about patisiran too.

Following slide, to support the ability for physicians to diagnose hATTR amyloidosis, we have the Alynlam Act Program offered in the U.S., which offers no charge genetic testing and genetic counseling through a third party. To date -- and this program has been running for about 3 years now, but to date, we have nearly 2,000 tests that have been submitted. And actually, over about 300 unique accounts have been established for this service. This is a U.S.-based program currently, but we are exploring similar programs in Europe as appropriate and as necessary given the health care systems are different over there.

Somewhat surprising for a rare disease as we'll see on Slide 54, the amyloidosis community has several -- actually many patient advocacy groups, both here in the U.S. and in Europe and even some in South America I've been aware of. I feel we are aligned with the advocacy groups in our goals of increasing disease awareness, enabling earlier diagnosis and the development of potential new therapies. And in conjunction with a company called, ThinkGenetic, we have recently hosted 3 patient care days, specifically for patients with ATTR amyloidosis here in the U.S. As an example of the invites we had, and actually Dr. Polydefkis spoke at one of these care days earlier this year.

Slide 55 shows the same graphic that Jared spoke to earlier, explains the disease is multi-systemic. What that means then as we try to think about commercializing and educating to similar specialists of the call points that we may have to educate is quite large. We feel given the predominant symptoms follow more on the polyneuropathy, but also some of the cardiomyopathy, neuromuscular specialists and neurologists will be our primary focus. However, understanding that patients with this disease may show up in other specialty areas also, gastroenterologists was mentioned already earlier and one of Dr. Polydefkis's cases, they also needed to think about how and when we can educate those physicians also, so tactics and priorities look different than for the neurologist.

On Slide 56, we have our first thoughts on our preparations here in the U.S. and our go-to-market strategy. Excitingly, patisiran, we expect to be the first Alnylam launch anywhere, and it will happen here in the U.S. we expect sometime in 2018. But it will be entering, we believe, a competitive market as inotersen is successful in their regulatory reviews. And in a market that has relatively low physician and patient awareness of the disease. As we build out our stakeholder facing teams that will interact with a wide variety of external stakeholders, including health care professionals, physicians, their office staff, genetic counselors potentially, but also patients and caregivers in appropriate way, advocacy organizations and of course with payers.

Given now ATTR amyloidosis is an ultra-orphan disease, we expect that our footprint, the size of our field forces would be commensurate with a small and focused orphan disease product.

In Europe, on Slide 57, we are actively building our presence there, focusing on the big 5 EU countries, but also given the endemic populations in Portugal and Sweden are focusing on those 2 countries in our first wave of priorities.

The country organizations will be led by country managers. And in those organizations, we'll include local sales and marketing, medical affairs staff, market -- and local market access personnel also. In the regional support and again, our Zug headquarters in Switzerland, we'll have regional support for market access, our general administrative supplies for finance, legal, et cetera, as well as supply chain function.

So going to conclusion here on Slide 58, in many ways, ATTR amyloidosis is like many other ultra-rare diseases. Patients with the disease are hard to find. And the true market opportunity is difficult to ascertain until treatment options are available and concerted efforts are in place to raise awareness of the disease and enable diagnosis.

Given the Phase II OLE data and the recent inotersen efficacy data, we are encouraged by the potential for positive APOLLO results in early fall. We are already preparing for commercialization of patisiran in our territories, and we're working with Sanofi-Genzyme to enable the delivery of patisiran for patients around the world.

The table on the bottom is just a reiteration of our development objectives for patisiran that we've laid out last year -- at the end of last year, early this year. We've already provided the final Phase II OLE data. Jared gave us a nice brief overview of that. And we expect the APOLLO top line results in mid- to late September with a presentation of the full suite of results at a conference in mid-Q4 of this year. And again, assuming positive data, we are planning aggressively to file the NDA by the end of this year with the [MAA] following shortly afterward.

With that, now I think our presentations are complete, so we'd like to move to some of the questions. So, I'll remind you, if you have questions, please if you submit those to us by clicking on the button through the webcast. And if I may, I think we may kick off this first question to Dr. Polydefkis. So with potential new therapies in the horizon, have you noticed any increase in individuals or families inquiring about the disease or seeking a diagnosis?

Unidentified Company Representative

Yes. It's been a pleasant surprise. Many patients that contacted me directly or gone through other family members expressing interest in these new therapies and that tracked with the behavior previously with family members almost didn't want to know the diagnosis because it carries such a poor prognosis. (inaudible) in just a few years.

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

That's an interesting point to follow up on. You said family members obviously may be affected by this disease. Are you seeing them more open to being tested or you have any examples, perhaps from your case 3 you mentioned, about how the family reacted to that new diagnosis?

Unidentified Company Representative

Yes, the people vary. Family members are generally much more adaptive to get tested genetically and be evaluated clinically. And some families are quite aggressive in following through, so that we can make that happen.

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

And then given the long and difficult path to diagnosis that you've laid out, what do you think that you as a physician or other physicians can do to increase that rate of diagnosis and shorten the time these patients have to go to get to a diagnosis?

Unidentified Company Representative

Yes, I think that's changed as well. Just like with the prospect of treatment makes the diagnosis -- we can do something about it. I know with my own experience, other members in our group, the people were making this diagnosis de novo much more commonly than we had in previous years. I think that reflects the fact that it's on our radar, that we're thinking about it more. We're more attentive to the variabilities, presentations. We have better tools (inaudible) to improving tools. We have tissue-type testing (inaudible) and improved availability of genetic testing. So making it much more -- much easier to make this diagnosis.

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

And following on from that, you mentioned the skin biopsies and actually making the first diagnosis at your institution by skin biopsies, what do you think is the feasibility of doing skin biopsies for diagnosis in the community setting?

Unidentified Company Representative

Yes, skin biopsies are very well cultivated. It's of similar (inaudible) shipped all across the world. It has been demonstrated in an open label APOLLO study. So it's doable. Skin biopsies are moderately invasive but certainly less invasive than other types of biopsies. So I imagine it'll be attractive with patients (inaudible) .

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

And then how do you think about staging tissue biopsies timing-wise relative to a genotype? Do you prefer 1 before the other? And if so, why?

Unidentified Company Representative

Well, the genotype demonstrates the susceptibility to the disease. At this point the question most vocal with us is when to start treating. I think with tissue types it demonstrates that the (inaudible) is starting to grow in terms of amyloid (inaudible) . How those tests are performed I think will vary based on patient preferences and age about your -- it makes sense that a 5-year-old won't be symptomatic for decades, but certainly with people (inaudible) the symptomatic period, I think genetic testing relatively (inaudible) tissue type to be attractive (inaudible)

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

And I know you have a genetic counselor in your institution. How do you utilize her in these discussions with potential patients?

Unidentified Company Representative

Yes, that's an excellent question. She's made available to all our patients and their families, and much of the time they'll see, she'll start educating them about the (inaudible) nature and the (inaudible) implications. Genetic counseling is a critical (inaudible) .

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

And then a question we -- and I mentioned it in my discussion, the challenge of understanding patients -- there are a number of patients that are true, or who are predominantly polyneuropathy versus kind of predominately cardio or the more likelihood of this mixed phenotype patients. Do you any ways you could estimate in your experience, in your clinic, kind of the percentage that falls in each one of those buckets, kind of predominately polyneuropathy, predominately cardiomyopathy or predominately mixed?

Unidentified Company Representative

I think increasingly the mixed phenotype is much more common. But obviously these patients, who might be predominantly cardiac or predominantly neurological, but it's relatively rare to have a patient with advanced cardiac disease and no evidence [polyneuropathy] in my experience.

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

Great. And Jared, if I may, on the endpoints for APOLLO -- couple of them anyway. What's -- what do you think the FDA is thinking about the Norfolk quality of life or the R-ODS endpoint in discussions you've had with them?

Jared A. Gollob - *Alnylam Pharmaceuticals, Inc. - VP of Clinical Research*

Well, I think the mNIS+7 is of course paramount and that's why it's our primary endpoint because its ability to show the impact of the drug and all of the different components of the polyneuropathy, motor sensory and autonomic. The secondary endpoint comes into play in terms of really showing the clinical benefit or the clinical meaningfulness of the effect of the drug on the polyneuropathy. And so I think from the agency standpoint, the Norfolk quality of life is a very important measure for helping them to understand what's the clinical impact -- clinical meaningfulness of an impact on neuropathy to the patient. The R-ODS, the Rasch-built Overall Disability Scale, has been used in other neuropathies -- polyneuropathies including inflammatory polyneuropathies, but this is the first time we're using it in hATTR amyloidosis. And, in fact, Dr. Polydefkis had discussed R-ODS with us early in the development of APOLLO and was one of the experts that recommended that we include this as a secondary endpoint. Because disability is such an important part of this disease and showing an impact on disability with a test like the R-ODS could be very impactful and really could further show the clinical meaningfulness of the drug in these patients. And that's the reason why it's included as a secondary endpoint. And the agency will see this for the first time with APOLLO as an endpoint, but our hope is that it will further reinforce the clinical -- potential clinical benefit in addition to what we hope to see with the Norfolk quality of life and some of the other endpoints.

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

Great. And going back to the Phase II OLE on Slide 38 and 39, where you walked us through the amyloid burden in the skin as well as the nerve fiber density. So it's always -- often a question of the trend seems quite positive through 18 months and then seems to change at 24 months. I wondered if you had any thoughts, Jared, first maybe, and then Dr. Polydefkis, we'd love to hear your thoughts also.

Jared A. Gollob - *Alnylam Pharmaceuticals, Inc. - VP of Clinical Research*

Sure. I think one important thing to remember is that the numbers there are small in the study. If you look at the end, under those bar graphs, the numbers are 19 to 22 patients. And so I think small numbers along with the fact that there's going to be some sample variability. Amyloid deposition is not going to be uniform throughout, it's going to be patchy. And even nerve fiber density is not going to be the same every place that you can go on biopsies. And so their expectation would be that there will be some variability from sample to sample and that combined with small patient numbers could well be the reason why at 24 months you see less of an effect, although you still see an effect. And I think, overall, what's most important here is that we are actually seeing a consistent effect on both amyloid burden and (inaudible) nerve fiber density at every time point. Even if there is some fluctuation or a para diminution between 24 months and 18 months, there still is significant effect at every time point. And I think also that very important inverse correlation that we're seeing between amyloid burden and nerve fiber density. So the lower the amyloid burden, the -- when we see a decrease in dermal amyloid burden, we see an increase in nerve fiber density, that connection further establishes sort of the biologic plausibility of what we're seeing and what these measures are really telling us. And I think all of that outweighs some of the fluctuation that we see at 24 months compared to 18 months. I'll let Michael further give his perspective.

Unidentified Company Representative

I'll answer that. I think the samples are small but the fact that there's just a decrease, I think is incredibly encouraging. If I'd been asked before this was done what I hoped to see, I would have been very pleased, very excited just to see stability. So the fact that there was a decrement in the amount of amyloid is very encouraging. And many of these results (inaudible) we're finding have also held up in a separate study with different patients. So I think the findings are robust albeit a small sample size.

Jared A. Gollob - *Alnylam Pharmaceuticals, Inc. - VP of Clinical Research*

And maybe I would just also add that we do have this as an endpoint -- as an exploratory endpoint on APOLLO. So we do expect to have a larger number of samples be evaluated. And our hope is that those findings will be able to confirm what we've seen here in the Phase II open-label extension study.

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

Great. Maybe one more question for you Jared. Obviously, the Phase II OLE has been a wealth of information and gives us some encouragement for APOLLO, but how would you characterize the patient populations in the Phase II OLE versus those in APOLLO? And how are they similar or if any way different?

Jared A. Gollob - *Alnylam Pharmaceuticals, Inc. - VP of Clinical Research*

Well, I think that the similarities include the fact that within the Phase II open-label extension study, we do have patients with mild-to-moderate polyneuropathy. Roughly, 40% of those patients have cardiac involvement. And if we look at this sort of mixed phenotype, which is not uncommon in this Phase II open-label extension study patients, we can see similarities really with what we're going to see on APOLLO. APOLLO will include an even wider range of neuropathy severity. It will include a wider range of mutations in patients from different geographic regions because it's a 225-patient study. And it will also include -- as we saw in Phase II open-label extension, it will include a substantial proportion of patients, roughly half of the patients or so, who will have evidence for cardiac amyloid involvement. So I think overall, there are probably more similarities than differences, but I think the major difference with the APOLLO study is that there will be patients with an even wider range of disease severity, more mutations and more geographic diversity compared to the Phase II open-label extension.

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

Okay. Good. Helpful. Another question about our commercial organization. And I'm going to take this one. Primarily in the U.S. And the question, if we would have a single sales force or approximately split sales forces based on the specialty call points. At this -- again, given it's a ultra-rare disease, multi-systemic disease, we find most patients are coming into tertiary care centers, there are multi-specialty treatment teams that work with these patients. Though at this point, we anticipate a single sales force at least here in the U.S. that would call on the appropriate physician and the given institution that may see these patients. The follow-up question there was do we expect to have in any different messaging for the different call point? In some ways slightly. Obviously, nuanced. If you're talking to a neurologist about cardiac involvement or what you look for in an echo, that may be inappropriate or at least fall on deaf ears. So to identify or describe these patients in terms -- in organ classes that a physician may think about or see every day will probably be necessary. Some other questions coming in. Jared, maybe you can talk a little bit more about the cardiac subgroup that we have defined in APOLLO. And what some of the exploratory endpoints we would see from those patients.

Jared A. Gollob - *Alnylam Pharmaceuticals, Inc. - VP of Clinical Research*

Sure. So the cardiac subpopulation in APOLLO will essentially be patients who have evidence -- echocardiographic evidence for cardiac amyloid involvement and will not have other conditions that can also contribute to heart wall thickening, like hypertension or aortic valve disease. In terms of what we're looking at in the cardiac subpopulation, the endpoints will be essentially very similar to the source of endpoints you look at in the cardiac subgroup, which was defined in a similar manner in the Phase II open-label extension study. So these will include echocardiographic measures, looking at wall thickness, systolic function, diastolic function, et cetera, with regards to cardiac involvement in terms of structured function and will also include cardiac biomarkers -- circulating biomarkers and notably NT-proBNP (inaudible) , which are checked [clearly] . Now it should be noted that essentially, we're doing these assessments on all patients on the APOLLO study, but the real analysis will be in those patients who have evidence for cardiac involvement at the time of study entry.

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

Excellent. Just one more question about the amount of discontinuations we've seen from the Phase II OLE study or APOLLO. We haven't been explicit about those numbers, but obviously, 25 of the 27 patients on the Phase II OLE did make it to the end of that 2-year study, and a very large majority of those moved over to the APOLLO OLE study and continued dosing. Some of them out for 3 years already or beyond. If there are any other questions coming in. That's about all we had for questions unless anything else. If not, I think we'll turn it over to Josh to conclude. And again, thank you very much Dr. Polydefkis, and thank you, Dr. Gollob

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Joshua Brodsky

Excellent. Thanks so much, Eric. And thanks again to Dr. Polydefkis and Jared Gollob. So this concludes our RNAi roundtable for today, and the replay and slides will be posted on the Alnylam website later today at alnylam.com/capella with the transcript to follow shortly thereafter. We look forward to your participate next Wednesday, August 9 at 12:30 p.m. Eastern Time, when we discuss the results from the investigation into the mortality imbalance from the ENDEAVOUR Phase III study with revusiran. And in the weeks that follow, to discuss additional programs from Alynlam pipeline of investigational RNAi therapeutics as shown here on Slide 60. For more details, please visit alnylam.com/capella. Thanks, everybody. Have a great day.
