Alnylam Pharmaceuticals Inc 2016 RNAi Roundtable: Patisiran and Revusiran for the hATTR amyloidosis Corporate Call

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CORPORATE PARTICIPANTS

Josh Brodsky, Alnylam Pharmaceuticals, Inc. - Senior Manager of IR and Corporate Communications

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

John Berk, Boston University Amyloidosis Center - Director,Clinical Trials for Familial Amyloidosis

Christina Lindsey, - Participant

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

PRESENTATION

Operator

Thank you ladies and gentlemen for joining today's RNAi Roundtable. We will be conducting two Web-based question-and-answer sessions during the webcast. (Operator Instructions).

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

Josh Brodsky, Alnylam Pharmaceuticals, Inc. - Senior Manager of IR and Corporate Communications

Good morning everyone and thank you for joining us for our RNAi Roundtable to discuss the progress we are making with Patisiran, Revusiran and ALN-TTRsc02 in development for the treatment of transthyretin-mediated amyloidosis.

I am Josh Brodsky, Senior Manager of Investor Relations and Corporate Communications at Alnylam, and with me today are Eric Green, Vice President and General Manager of the TTR Program at Alnylam; John Berk of the Boston University Amyloidosis Center; Christina Lindsey, a patient living with hereditary ATTR amyloidosis, and Jared Gollob, Vice President of Clinical Research at Alnylam.

I will be turning the call over to Eric in a moment who will provide you with a brief introduction. But first a few comments. Today's RNAi Roundtable focus on our TTR programs is the first in a series of roundtables that we are hosting this summer and early fall. Today's event will end at around 1:00 PM Eastern time. We will have two Q&A sessions and you may submit a question at any time during the webcast, (Operator Instructions).

Eric will moderate a Q&A session with Dr. Berk and Ms. Lindsey and then another with Jared at the conclusion at the conclusion of their presentations.

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 turn the call over to Eric.

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

Thank you, Josh, and thanks everyone for joining us today to hear about our TTR programs. As all of you know, Alnylam 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 Alnylam's efforts, RNAi is a clinically proven approach.

Alnlyam has developed a pipeline of products focused in three strategic therapeutic areas or STArs. These are genetic medicines, cardio metabolic diseases and hepatic infectious diseases representing a range of disease opportunities from rare to common to global diseases.

On slide eight, you will see that each of the specific programs listed by STAr showing that we now have 10 products in the clinic and six of them having achieved human proof of concept already. Today we will focus on our three TTR programs. Patisiran and Revusiran are both in late stage clinical development while ALN-TTRsc02 entered into the clinic just last month.

On slide 10, you can see from our agenda Dr. Berk from BU Amyloidosis Center will provide an overview of hATTR amyloidosis. After he speaks, Christina will share with us what it is like to live with this disease including the impact on her family. After Christina, we will have a Q&A session with both Dr. Berk in Christina. So please throughout the presentation remember to submit your questions as we go. Dr. Berk?

John Berk, Boston University Amyloidosis Center - Director,Clinical Trials for Familial Amyloidosis

Thank you very much, Eric. So the transthyretin amyloidosis are a result of mis-folding of a protein depicted by this ribbon diagram and as you can see, the protein preferentially circulates as a tetramer or four identical proteins combined. It is composed of 127 amino acids, it is primarily produced by the liver although there is some production by the retinal epithelium as well as in the brain by the choroid plexus. Next slide please.

The transthyretin amyloidosis are of two varieties. One mis-folding of a normal or wild type protein previously called senile systemic amyloid and now referred to as wild type disease. And secondly, familial transthyretin amyloid which is conferred by a variant protein that is modified by point mutations with over 130 amino acid substitutions reported to date. These variant diseases exhibit autosomal dominant genetics and both the wild type and familial transthyretin amyloid diseases are lethal with survivals being between three and 15 years after presentation.

At the bottom of the slide, you can see a depiction of the spectrum of protein confirmations. As previously mentioned, the native TTR preferentially circulates as a tetramer and with the introduction of either aging components that alter the stability of the protein or the variant mutations that occur, there is destabilization of the tetramer dissociation of monomers which at that point can mis-fold and for oligomers and then ultimately amyloid fibrils. Next slide please.

On this slide, we see the spectrum of mutations that have been identified in the TTR gene. As you can see from the five prime untranslated region or the amino terminus all the way to the three prime untranslated region end, there are multiple sites. V30M or valine 30 methionine is the most prevalent mutation in the world and confers a preferential peripheral neuropathy. In contrast at the other end of the gene, you can see a mutation that involves position 122 and there is an amino acid substitution of isoleucine for valine. And this mutation is carried by more than 1 million African-American people in the United States.

Next slide please.

The spectrum of TTR disease is quite wide and going from bottom to top what you can see is that the predominant manifestation of disease is a symmetric length dependent sensorimotor peripheral neuropathy. This can be accompanied by a separate network of nerves that are affected and this is the autonomic neuropathy that controls erectile function, bladder contractility and blood pressure control upon standing. In addition, it can affect the motility of the GI tract.

So with peripheral neuropathy autonomic neuropathy, GI manifestations may occur. Rarely there is kidney involvement and in some mutations we see involvement of the brain with the protein being generated in the choroid plexus and deposited in the brain itself. We will discuss cardiovascular manifestations in a few minutes. Next slide please.

The symptoms at presentation for peripheral neuropathy are predominantly those of the sensorimotor variety, so pain, tingling occurs in a vast majority of people, loss of touch and pain is associated. In addition, the autonomic manifestations are prominent and they can begin with changes in GI motility of constipation or diarrhea. There can be erectile dysfunction, lightheadedness upon standing and changes in sweating or salivation and in a rare number of cases, problems primarily with urination.

The age range of first symptoms is quite wide and the symptoms of peripheral neuropathy are common to many other neuropathies making diagnosis sometimes quite challenging. If there are autonomic symptoms and particularly when those are coupled with family history, it should signal considerations of TTR disease. Next slide please.

This is a favorite elevator depiction of the various mutations than what it captures is the variety of end organ involvement that can occur with particular mutations. So we speak of genotype dictating phenotype in these diseases. And as you can see MET 30, tyrosine 77, glysine 89 and 64 are ones that mutation particularly targets neurologic manifestations. Next slide please.

In contrast there are a number of mutations that target the heart involvement and those are isoleucine 122, leucine 68, methionine 111 and alanine 60. Notably in the United States, 3% to 4% of African-Americans are carriers of the genotype of isoleucine 122 and there is geographic distribution of mutations as evident with alanine 60 in the UK and US, methionine 111 in Denmark, and leucine 68 in Italy. Next slide please.

Where are these people? What is the epidemiology of TTR amyloid? In the United States it is estimated there are about 3200 people with active disease and in Portugal which is the epicenter for MET 30 disease in the world, there are estimated to be about 2000 patients and you can see the numbers for other locations. So there are a majority of patients in the European Union. Next slide please.

In order to develop new drugs for treatment of these diseases it is important to know what the natural history is and only with that information can clinical trials be properly designed. This slide captures data from patients who were untreated, either from the placebo arm of the tafamidis or diflunisal trials or a natural history study that was reported by David Adams from France in 2015. You can see the various TTR genotypes that were involved in these groups; the age present at enrollment of the studies, the stage of disease neurologically and then a neurologic impairment score of the various subjects involved in the studies.

Finally in the last column, the rate of neuropathy progression and it is notable that the tafamidis study which is in the first row is a little bit different than the NIS progression noted for the other groups and that is a reflection of the very early disease that was involved in that study. Next slide please.

Cardiomyopathy has its own set of issues and manifestations. Amyloid when it infiltrates the heart thickens the ventricular wall impairing relaxation by stiffening the ventricle and subsequently affecting the ability of that ventricle to contract, reducing the amount of blood that is pumped with each contraction. Shortness of breath ensues because there is an elevation of filling pressures, essentially a backup of fluid that is not being properly forward flowing with contractions. They may result lower extremity edema, increased pressures in blood vessels and ultimately some swelling of the liver, fluid collections around the lungs and in the abdomen and these are all signs of congestive heart failure.

In addition to affecting the muscle of the heart, the wires of the heart can also be involved altering the conduction of electricity and the coordination of contractions. Abnormal rhythms such as atrial fibrillation are characteristic. We use the BNP or N-terminal pro-brain natriuretic peptide as a cardiac biomarker which permits us to monitor the course of disease. It is effectively a measure of congestive heart failure. Next slide please.

How does this disease, transthyretin amyloid affect survival? We will look at wild type and then the familial forms of disease.

In this, this graph depicts the survival so you can see that there are two major groups here that are considered. One is Columbia University's experience and then also the National Amyloid Center from the UK. The purple graph is the pooled data and as you can see in this Kaplan-Meier graph, there is a slow but steady decline in survival and permitting a calculation of median survival which is actually less than three years. Next slide please.

In contrast to the wild type disease you see in the hereditary cardiomyopathy a biphasic or two-phase survival curve. So initially it follows this slow decline that we saw in the last slide and then at approximately 25 to 28 months follow-up, we find that there is a steeper decline in the survival and that the experience at Columbia and the National Amyloid Center mirror one another as they are parallel. Again, the median survival is quite short. Next slide please.

How does this change, how does this affect on survival alter the care of patients in their course through life? We can measure that through cardiovascular hospitalizations. These are data collected from the Columbia experience and you can see in the left graph, wild type patients and in the right graph, the hereditary cardiomyopathy patients. There are a couple of distinctions to be made here. The graph captures the number of patients on the y-axis and the frequency of cardiovascular hospitalizations on the x-axis. You can see that the familial patients rarely avoid hospitalization and over time that they require more hospitalizations than the wild type patients. Next slide please.

In measures of function, hopefully we will reflect the true course and biology of disease. The six-minute walk test is something that has been used in cardiomyopathy trials over the years and is a standard measure. The graph here captures the change in distance walked from baseline and then the x-axis captures the data over time zero, six, 12 and 18 months.

What you can see is that there are divergent experiences between the wild type and the hereditary patients. In the wild type population, there is a slow, steady decline which is reminiscent of the survival data that we looked at previously. In contrast, the hereditary group has a slow decline initially in six-minute walk distance but then it suddenly declines at a more rapid rate than we saw with the wild type. Next slide please.

So to summarize, we have an overview here of the process and biology of TTR with generation from the liver, circulation as the homotetramer, dissociation to the monomer which can then miss fold in formation of fibrils. And going from right to left on this slide looking at therapeutic options, disruption of amyloid fibrils that have formed and deposited is the intent of the doxycycline and bile salt derivative, TUDCA preparation. The data from these are several Phase 2 studies which have mixed results to date.

Secondarily is stabilization of the TTR tetramer as it circulates and there have been several Phase 3 studies that have reported similar results, tafamidis and diflunisal and then a third agent, Tolcapone, which is being considered for trial but has a similar mechanism.

Finally, interventions to alter TTR synthesis and initially the first genetic experiment was orthotopic liver transplantation which proves effective in patients particularly with MET 30 mutation when performed very early in the disease. But there have been considerable complications of disease progression in patients with other mutations at later stage of disease when transplant occurs.

Finally and most importantly, gene silencing as an avenue to suppress the TTR circulating levels to the point that there is nothing available for amyloid formulation to occur and these include the anti-sense oligonucleotide preparation of Ionis and the focus of today's roundtable, the RNAi product of Patisiran and Revusiran. The availability of disease modifying therapies is limited as discussed above and so there is a rather large unmet medical need for additional therapies. Thank you very much.

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

Excellent. Thank you, Dr. Berk. I will now turn the call over to Christina to share her story. Christina, don't forget to turn your phone off mute and your first slide will be up so you are welcome to start.

Christina Lindsey, - Participant

Perfect. Thank you so much for allowing me to share my journey. I am Christina Lindsey and the above picture is my family. As you can see, we live life to the fullest and enjoy every moment we have to together. We are currently living in Virginia via the Marine Corps. Next slide please.

Defining me can be very difficult. First and foremost, I am a wife and a mother. I have four children Holly, Ashton, Anna and Jake and I also gained a bonus son after my middle daughter got married a couple of months ago. I am an untraditional teacher who educated all four of my children at home. Yes, I home school. My eldest has severe learning disabilities and I quickly realized that she would thrive from one-on-one education.

I was told that she would never graduate high school so the challenge was on. All three of my older children are now in college. Jacob is the only one I am currently teaching at home and it worked out beautifully because on Jacob's 10th birthday, we found out that he had a brain tumor. It has been removed and he is doing fantastic. However, his condition causes us to have frequent flyer miles to multiple specialists and doctors appointments. School on the go is necessary for us.

My husband is a career Marine and he has been active duty for over 22 years. Over the past four years, he has been deployed three times making me a very busy mom. Like most military families, we have been stationed far away from our immediate family. This leaves all of the responsibility to one person. This task can often be overwhelming and exhausting yet you have to stay strong for the children.

I have several certifications in physical fitness training, and Associates degree with kinesiology background. I am just four weeks short of graduating again with my Bachelors degree in healthcare administration. I decided to change my career path after I started felling this (inaudible) neuropathy. My certifications had stemmed from my love of running, kickboxing and cross fit style workouts but neuropathy, it was hard. I could no longer do the same things that I used to do. I used to be able to push out a morning workout and do all of my activities and then come home and run in the evening. This was no longer what I could do and this leads me to my next bullet point.

I am a patient living with TTR amyloidosis. Family ties run deep with the severity of amyloidosis. I'm sorry, next slide.

Family ties run deep with disparity of amyloidosis. While this disease is autosomal dominant, the prevalence of the disease seems to be even stronger as the generations move forward. The first time I had ever heard the word amyloidosis is when my grandfather died. I was only 10 or 11 at the time. Given the fact that his two brothers also passed from this disease all at early ages, I was told that this disease would only affect the men on the [McElliot] side of the family. This would definitely not be the case.

In 2003, my aunt decided that she would be gene tested. She was positive for both the gene and the tissue test at the age of 45. My father had the opportunity to be tested but declined out of fear of what one doctor had told him about a liver transplant. I chose to be gene tested, my testing came back positive. I still remember the phone call with Dr. Skinner; she is such a compassionate woman and was trying to help me cope with not only my own results but with the results that I would have to convey to my father.

My father realized that there was no denying the results and went in for further testing where he tested positive for both the gene and the tissue testing. Both he and my aunt received domino liver transplants within a few months of each other. Both are 10 years plus post-op and are doing really well. My father is now the oldest living person on the McElliot side of the family at the age of 65.

I have two younger brothers who also tested positive for the gene and are currently experiencing symptoms. They are both being followed by an amyloid specialist in Boston. My cousin, Dawn, who made the fabulous gene chart on the next slide, also tested positive for the gene. She is not only an amyloid patient but was the caregiver for her mother through this horrible disease. Her mother passed at a young age of 51.

Dawn is my partner in crime. We go through this disease together and we stay educated on everything amyloid. She helps encourage me in the hard times, we laugh at jokes a lot and we try to make light of a very serious and heavy situation. I don't know what I would do without her. She is like a sister that I never had. Together we do have hope for the future.

Even with hope, sadness sometimes overtakes you. A huge burden I have on my heart is the reality that my 18-year-old daughter, Anna, is geno positive. We had not planned on testing our children until much later in life when it became their decision. Anna

started having symptoms of idiopathic neuropathy. She has seen nine neurologist and a neurosurgeon. She has had three surgeries on her arm to release and transpose her ulnar nerves. All have failed. She now had symptoms of autonomic neuropathy and has to sit down in the shower to prevent a fall.

While there are no clear biomarkers for this disease, experts suggest that she is too young for disease onset. Her diagnosis remains guarded as you truly can't rule in or out amyloid. Meanwhile, we continue to search for alternative reasons for her symptoms. Next slide please.

This is the gene chart that Dawn composed. The chart will take you back six generations in our family history. This visual allows you to see how deep and devastating the disease is to our family. My father's generation is located on 4D. I am located on 5C with my children on 6C and Dawn is shown on 5A. Next slide please.

As I mentioned, I was gene tested in 2003 after positive testing baseline studies were done. Early symptoms started as bilateral carpal tunnel and a lack of hot and cold symptoms to my feet. I have seen a multitude of doctors in relation to this disease to include neurologists, cardiologists, ophthalmologists, neural ophthalmologist, gastrologists, pulmonologists, oncology, physical therapy, speech, pathologists, urologists and hematologists. I have been subject to multiple x-rays, scans, blood works, MRIs, biopsies, endoscopies, colonoscopies and the list continues.

This February the military moved our family from California to Virginia and this meant that I had to find all new specialists and physicians in the local area to handle my care. You even meet doctors who know about the disease or don't know about the disease and don't care to know about the disease or who think they are experts on amyloid and will tell you all of the wrong information. But on a rare occasion, you will get a doctor who admits they know nothing but are willing to listen to your knowledge and research your disease. These doctors are far and few between and should be considered rare diamonds in a pile of coal.

I have yet to show positive on a tissue test but have been diagnosed clinically. Over the past year, my symptoms have progressed faster than I had ever hoped. I have neuropathy in my feet and my legs and in both arms and this makes it difficult to do a lot of things to include driving. When I drive all four of my limbs go numb. I have G.I. symptoms that include interchanging diarrhea and constipation. I choke on liquids, I have bladder incontinence and as of last month, I experienced my first bowel incontinence.

I have night blindness caused by retinal damage so I can no longer drive at night. I have depression anxiety of what is happening now and the anticipation of what is going to happen in the future. Yet I can never show the fear, my family and cousin will lose hope.

I have extreme fatigue and this one is huge for me. I have to take three naps a day just to function. As I mentioned before, I am a busy home school mom with children that have special medical needs. I have to drive them to and from their appointments but the energy level is often not there. If I go to the post office or the grocery store, all of my energy is gone. I have to come home and take a nap and recharge before moving onto the next thing. This quality of life makes it nearly impossible to do anything beyond necessities.

My family is trying to find a new normal as they watch their mother's health deteriorate and not be able to do the fun stuff that I once did. My plan was to help offset some of the cost of the medical by entering the workforce. As I assessed my symptoms and constant back and forth to the appointments for myself, I realized my options are limited. I have to consider things like not driving at night, combating fatigue, how close is the bathroom, flexible hours and so on. I wonder if there is even such a job out there for me.

The worst part of this disease is the guilt, the guilt of knowing that you have passed this devastating disease to your children is even more than one can grieve. I watch my daughter fall apart with the foreknowledge of one day that she might have this disease and if the disease is already active due to her symptoms and I fall apart on the inside. I can't even show how scared or devastated I am on the outside in fear that she may give up hope. I'm sorry, next slide.

Even with all the devastation, I can still carry on with a smile because I have hope for the future generations. With technology advancing every day, I hope for better treatment options and quality of life. My hope is that there are biomarkers for clear diagnosis in the future. It is necessary to have a clear indication of early disease onset. One of my greatest fears is that my daughter has active disease yet she is not offered any therapeutic options for lack of not knowing if the diseases active. Biomarkers could eliminate so much of this anxiety anticipation in the disease. My hope is for delayed disease progression and ultimately eradication through improvement therapies.

I saw something by an unknown author made the statement that said -- hope turns into faith and faith turns into miracle and we are definitely holding on for a miracle. I just want to thank each and every one of you for listening to my journey and investing so much of your time and passion into our lives. Your work is completely appreciated. Thank you.

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

Thank you, Christina, for sharing so freely your experiences. This is obviously very moving and I very much appreciate it. We will now open up to questions on the webcast for Dr. Berk and Christina. Please remember you can submit your questions, or you can ask a question button just above your slide window in the webcast player.

If I may, Christina, can I ask you a question to get started? What if any therapies have you tried to manage some of your symptoms?

Christina Lindsey, - Participant

To manage symptoms, I am currently on diflunisal and also on gabapentin for the neuropathy and I'm trying to think what else I am taking. The green tea extract I believe it is EGCG. So so far, that is what I am on. I've tried medications for urinary incontinence and it did not work. I am currently taking Adderall to help combat fatigue and Zomig and Zofran and Botox as well for the chronic migraines.

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

Are you considering a liver transplant and if so, yes, and if not, how come?

Christina Lindsey, - Participant

Well, I'm really trying to hold out for the next generation of drug before I consider a liver transplant. If symptoms progress or accelerate faster than I had hoped, I might consider it. Liver transplants as you know are very risky and come with a lot of drug

maintenance and the mortality rates for liver transplants in the long-term are not super great.

I was also told by an expert that progression can still happen with a liver transplant given the good TTR proteins may stick to the amyloid proteins and possibly shutting down the other organs. I am sure that Dr. Berk could give more information on that. That is kind of where I am standing. I am just kind of waiting for the next line of medication to come out. I feel comfortable being on stabilizers at this point.

Obviously like I said if things were to accelerate then I might have to reconsider but I think right now given the information that my specialist has given me, I think I will just kind of hang on and wait.

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

Okay, thank you. Maybe a transition then to Dr. Berk. When if ever do you recommend a liver transplant to your patients who are additional to what Christina said, any pros and cons you see from the clinical side?

John Berk, Boston University Amyloidosis Center - Director,Clinical Trials for Familial Amyloidosis

The first liver transplants were done in 1990 so we are dealing now with now I think about 25 years of experience and there have been over 2400 reported liver transplants. The majority of that experience is in Portugal and other parts of the EU. And the growing recognition is that the one mutation that responds best to liver transplantation when done early in disease is the Met 30 mutation. That is the mutation that is specific to Portugal, is present in Sweden although even in those two different countries, there is early disease onset which is Portugal and (inaudible) which is Sweden.

When you talk about other mutations, the outcomes are not as good and the complications of disease progression that Christina mentioned become a real issue.

For people in Christina's family with that mutation, there is an additional complication because there is effect on the other side of the blood brain barrier with amyloid depositing called leptomeningeal disease and in those patients the concern is that effective liver transplant with complete eradication of the mutated protein may not be sufficient because there will be continued variant protein produced in the brain.

So it is a difficult decision. It is interesting in her family that there have been some long survivors with liver transplantation. So again, it seems most applicable to people who have Met-30 disease and very early onset.

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

Okay, thank you. Christina, another question that came in, have you noticed any difference since you started on diflunisal?

Christina Lindsey, - Participant

I personally have not noticed any difference but my last visit to my doctor's office did reveal that there was some at least a halt in the neurological aspect of it, maybe even bringing it back some, making it less. But personally, I don't see it but according to the neurological exam, there was some at least stabilization.

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

That is great.

John Berk, Boston University Amyloidosis Center - Director,Clinical Trials for Familial Amyloidosis

I think that is actually an important question. Speaking about TTR protein stabilizers versus gene silencers and the experience with the TTR protein stabilizers is that when effective, they will prevent progression of disease and that often there is some very slow progression that is noted over long periods of time.

In contrast, the TTR gene silencers if there is truly a dynamic interaction between the circulating TTR levels and what is deposited in end organs, there is potential of improvement over time and indeed the Phase 2 data from Alnylam with the 24-month experience which I believe you will be talking about later, suggests that there is actual improvement in some sensory components of the neurologic assessment and that would be a rather dramatic departure from the experience with the TTR protein stabilizers.

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

Excellent, thank you. Dr. Berk, how do you go about diagnosing a patient? When a new patient comes into your clinic, have they already received a diagnosis of ATTR amyloidosis and if not, what are the key symptoms that typically drive them to your office?

John Berk, Boston University Amyloidosis Center - Director,Clinical Trials for Familial Amyloidosis

So it is a little bit of a two phased response that in the past with really little therapeutic options and not a lot of interest by primary physicians on making diagnoses, people would be referred only when amyloid had been detected and TTR had been determined by typing. What we find now is that the interest in identifying people is increasing and in a predictable fashion as therapeutics are being established. And we see by screening ultrasounds, more and more people being referred simply with the findings consistent with amyloid cardiomyopathy, not with a diagnosis having been made. And whether that is from echo or cardiac MRI, it does afford earlier identification of people, it makes it a little more challenging for us to actually do the diagnostics in a short period of time.

Neurologically it is a little more complex because we don't have an easy screening test such as echoes so we rely on neurologist and primary care physicians to recognize potential manifestations of amyloid neuropathy.

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

Great. There is a question about one of the stats you had on one of the slides, potentially 1 million V122Icarriers but yet we think worldwide there's only about 40,000 patients with hATTR amyloidosis with cardiomyopathy. What are your thoughts on why the discrepancy in the numbers?

John Berk, Boston University Amyloidosis Center - Director,Clinical Trials for Familial Amyloidosis

The question really speaks to the issue of prevalence and penetration. So we know that between 3% and 4% of African-Americans

in the United States carry the mutation for V122I. However, what is quite unclear is the number of people who have the mutation who end up manifesting disease. Because this mutation confers disease with onset typically 65 years and older, it can be hard to separate out this population which is often challenged by hypertensive heart disease and congestive heart failure from those who have thickening of the heart not a response to hypertension but from amyloid infiltration.

So the simple answer is a lot of people have the gene abnormality, don't know how many are going to go on to express disease and it is becoming more and more clear that it is probably significantly less than 50% of the people will express disease.

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

Thank you. Maybe the last question if I may to Christina. Is there anything you would like to say to people out there that may be listening to this now or later that have similar symptoms to you but for some reasons may not want to get tested for amyloidosis. Do you have any recommendations or thoughts for them?

Christina Lindsey, - Participant

That is hard because so many people have fear for different reasons. I would just say that you can't ignore the disease despite how scary that it may be, you need to be tested to either rule it in or rule it out. The treatment options are different now, there are stabilization and there are new treatments on the horizon. You just cannot not get tested. You have to get over your fear and just test.

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

Excellent. I want to thank you very much for the questions and for Dr. Berk and for Christina to be able to share the overview of the disease and most importantly to Christina, thank you for sharing your personal story. It is very much appreciated. I think it is incredibly important that we remember and we at Alnylam why we are developing these products and it is with the hope of positively impacting the lives of patients with ATTR amyloidosis and their families. Thank you.

Christina Lindsey, - Participant

Thank you so much for having me. I appreciate the opportunity. It is very scary to open up so much but I think it is important to get the awareness out there. So again, thank you so much for allowing me to share my story.

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

Of course. Thank you. We will now move on to our TTR programs. So we will now discuss the three programs, Patisiran, Revusiran and ALN-TTRsc02. I will start with a brief overview and then Dr. Jared Gollob, our VP of Clinical Research and responsible for the development of all three programs will review the current data from our two late stage programs anyway, Patisiran and Revusiran.

So on to slide 36 and as described by Dr. Burke, ATTR amyloidosis is a progressive and life-threatening disease caused by the mis-folding of the transthyretin TTR protein that accumulates as amyloid fibrils in multiple organs. As discussed, the hereditary form of the disease that is caused by mutation in the TTR gene may affect about 50,000 people in the world.

Now as was also mentioned by Dr. Berk, there is emerging data out that suggests that patients that present primarily with polyneuropathy or primarily with cardiomyopathy, many of those patients also present with symptoms across the disease spectrums including autonomic symptoms and indeed have a mixed phenotype.

Our hypothesis for the treatment of ATTR amyloidosis with RNAi therapeutics is quite straightforward. By reducing the production of both wild type and mutant TTR in the liver, the levels of unstable circulating TTR proteins are reduced preventing new amyloid fibrils from being deposited and potentially allowing the body to clear existing amyloid. This clearance could potentially lead to the stabilization or improvement in neuropathy and or cardiomyopathy.

On slide 38, you will see all three of our TTR programs demonstrate our continued commitment of innovation for patients with this disease.

Patisiran is the most advanced product with enrollment in our APOLLO Phase 3 study completed earlier this year. Revusiran is the most advanced siRNAi GalNAc conjugate product in Alnylam's pipeline and with some patients have now been dosed for 18 months. The ENDEAVOUR Phase 3 study with Revusiran is currently enrolling.

And ALN-TTRsc02 utilizes our enhanced stabilization chemistry or ESC chemistry and entered into the clinics last month.

On slide 39, you can see the details of our APOLLO phase 3 study. We have enrolled 225 patients with hATTR-PN in this randomized double-blind placebo-controlled study evaluating the effects of Patisiran on neuropathy progression as measured by the modified NIS+7 score at 18 months of treatment.

Jared will discuss some baseline demographics from the study in a few minutes. We expect a data readout from APOLLO in mid-2017 and if positive we will work diligently to file an NDA and an MAA in the play 2017 timeframe.

Slide 40 shows a very similar chart for the ENDEAVOUR study, a randomized double-blind placebo-controlled study to evaluate the efficacy and safety of Revusiran in patients with the hereditary ATTR with cardiomyopathy. The co-primary endpoints for this study are the change from baseline at 18 months in the six-minute walk test and also in TTR knockdown. ENDEAVOUR will provide definitive evidence about the impact of RNAi therapeutics in hereditary ATTR amyloidosis with cardiomyopathy. We expect to complete enrollment yet this summer and report data therefore in early 2018.

ALN-TTRsc02 presents the potential to have a best-in-class profile. With this product we expect to be able to have quarterly injections which will be a significant improvement from the over 50 injections per year needed with both Revusiran and with a competitive program. We expect this major advance to improve compliance and we hope therefore efficacy in addition to potentially overall tolerability.

The Phase 1 study in healthy volunteers started last month and we expect to report initial clinical results from this program in late 2016. Ultimately, we believe ALN-TTRsc02 will emerge as the best in class product for the treatment of the entire spectrum of ATTR amyloidosis.

With APOLLO data coming in mid-2017, we have been actively preparing for commercialization in our territories and through our alliance with Sanofi Genzyme, Alnylam will solely commercialize Patisiran in the United States, Canada and Western Europe. And Sanofi Genzyme will commercialize Patisiran in the rest of the world.

We have started to build our own internal commercial organization with a head of Europe and Canada starting earlier this year and we are actively recruiting for key in-country commercial leadership roles in our major markets. Indeed in the US, we have our medical science liaison team or MSLs already in place and are building out our medical affairs organization in Europe yet this year.

Jared will now discuss our latest data from both Patisiran and Revusiran. Jared?

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

Great. Thank you, Eric. So on slide 44, the Alnylam programs in ATTR amyloidosis are designed to cover the full spectrum of disease seen in these patients. The two programs that are in late stage development currently are the Patisiran programs aimed at patients with hATTR-PN, many of whom also have cardiomyopathy as well as the Revusiran program that is being developed currently in patients with hATTR-CM.

In this section I'm going to review the key presentations that were recently highlighted at the International Society for Amyloidosis meeting in Uppsala, Sweden earlier this month. These reviews will include a review of the interim 24-month data from the Patisiran Phase 2 open label extension study, a review of the baseline characteristics from the ongoing Phase 3 APOLLO study as well as interim 12-month data from the Revusiran Phase 2 open label extension study.

Starting with the Phase 2 open label extension study update, slide 45 shows the design of the open label extension study. This study was for patients who had previously been treated on the Phase 2 study, all patients on the open label extension study received Patisiran at a dose of 0.3 milligrams per kilogram administered once every three weeks for up to two years. Multiple efficacy endpoints as well as safety were evaluated on this Phase 2 open label extension study. Many of the efficacy measures were performed every six months. In addition, serum TTR levels were performed on a regular basis.

Many of the clinical endpoints on the Phase 2 open label extension study are also in the APOLLO Phase 3 study and including the APOLLO Phase 3 primary endpoint, the mNIS+7 therefore the Phase 2 open label extension study does give us a potential window into understanding the activity of Patisiran in this patient population and the potential for Patisiran to impact the disease in patients being treated on the APOLLO trial.

Slide 46 shows the demographics and exposure data for the patients treated on the Phase 2 open label extension study. There were 27 patients who were treated on the study with a median age of 64 years. Most of these patients have the VAL30Met TTR genotype and most of these patients had FAP stage 1 disease. The majority of patients came onto the study receiving either tafamidis or diflunisal concurrently. The current tetramer stabilizer use has decreased so that there are now 14 patients on tetramer stabilizers compared to 20 patients who became the study on tetramer stabilizers. Patients have received a median of 35 doses to date with a mean treatment duration of 24 months.

Moving on to the safety summary on slide 47, the table on the left shows the common adverse events seen in at least 10% of patients. Many of these adverse events shown in the table on the left were unrelated to study drug. There were six patients who had nine reports of serious adverse events none of which were related to study drug. The majority of adverse events seen were mild or moderate in intensity, the most common related adverse events included flushing, seen in 22% of patients and infusion related reactions seen in approximately 18.5% of patients, all of which were mild.

Importantly, there were no clinically significant changes in liver function tests, renal function or any hematologic parameters including no changes in platelet count.

The next slide, slide 48, shows the fact that we did not see any significant decrease in platelet count in patients throughout their treatment on study nor have we seen any association between the degree of transthyretin knockdown and any modest change in platelet count that have been seen on the study.

Slide 49 looks at TTR knockdown over time in patients on the trial. As you can see, there is rapid and robust knockdown of serum TTR with a mean serum pre-dose TTR knockdown of approximately 80% and a mean maximal serum post dose TTR knockdown of 93% and you can see that this knockdown is maintained out past 24 months in patients treated with Patisiran on an every three week basis.

Importantly, we saw similar TTR knockdown in patients on Patisiran alone as well as in patients who were on Patisiran in addition to tetramer stabilizers.

In addition to safety and TTR lowering, we also look at various clinical measures, one of the most important of which is the mNIS+7 composite neurologic impairment score which is also the primary endpoint on the APOLLO Phase 3 study. The mNIS+7 essentially encompasses all the different components and aspects of TTR related neuropathy including measures of motor strength and weakness, measures of reflexes, measures of sensation as assayed by the quantitative sensory testing as well as measures of nerve conduction and autonomic function by postural blood pressure.

The mNIS+7 score can be as high as 304 points. An increase in the score indicates worsening of disease, a decrease indicates improvement.

Slide 51 shows the summary data for mNIS+7, the change in mNIS+7 over a 24-month period. The graph at the top shows the mNIS+7 value at baseline which is zero months and then at six, 12, 18 and 24 months for each individual subject on the study. The table at the bottom shows the summary data and you can see that in all of these patients there was a mean 6.7 point decrease in the mNIS+7 at 24 months in the 24 patients evaluable patients at 24 months with a median decrease of minus 6.8.

As you can see when you look at the various subcomponents of mNIS+7, there was a consistent stabilization or improvement across all the different subcomponents with the greatest decrease or improvement seen in the quantitative sensory testing component which measures such pressure and heat pain.

In addition when you look at the graph on top and you look at the mNIS+7 on the y-axis, you can see that patients with higher mNIS+7 scores at baseline do just as well as patients with lower mNIS+7 scores at baseline suggesting that the drug is able to have this impact regardless of the degree of disease severity at baseline.

Slide 52 now presents the data in a waterfall plot. We are now looking at the data at 24 months for individual subjects and we are

looking at the change in the mNIS+7 score for individual subjects at 24 months. You can see that in 17 out of 24 patients or 71%, you see either no change or an improvement or a decrease in mNIS+7 score at 24 months compared to baseline.

This compares very favorably to what has been seen historically in either natural history data sets or in datasets from Phase 3 studies. In the graph on the right, you can see that the expected change in mNIS+7, the estimated change in mNIS+7 from a published natural history study is approximately 26 points at 24 months. The estimated change in mNIS+7 from the placebo arm of the diflunisal Phase 3 study was almost 30 points at 24 months and even patients treated with diflunisal still had a 9 point increase in the mNIS+7 at 24 months whereas the patients on the Patisiran Phase 2 open label extension study had a mean minus 6.7 point decrease in mNIS+7 at 24 months.

Slide 53 now looks at the correlation between the degree of TTR knockdown and the change and mNIS+7 at various time points over the study. On the x-axis, we are looking at the percent TTR knockdown seen at 17 days following the first dose of Patisiran and on the y-axis we are looking at the change in mNIS+7. And you can see that across all of these time points, there is clear correlation between the degree of TTR knockdown and the extent of mNIS+7 change. Notably patients with more TTR knockdown have more of a decrease or drop or improvement in the mNIS+7. This correlation between the extent of TTR knockdown any change in mNIS+7 was significant at six and 12 months and approached significance at 18 and at 24 months.

Slide 54 looks at another efficacy assessment that was performed on this study. This is now looking at nerve innovation or nerve fiber density that was measured within skin punch biopsies. The skin punch biopsies were performed in the leg in both the distal thigh and in the distal leg so looking at the proximal and distal portion of the lower extremity. And the graph on the left shows the change in sweat gland nerve fiber density either in the distal thigh which is the dark triangle or in the distal leg which is the light blue triangle.

And what you can see is that in the distal thigh starting at 12 months, there is a significant increase in sweat gland nerve fiber density that is maintained out to 24 months. In the distal leg, we see an increase in nerve fiber density that becomes significant out at 24 months. And in the panel on the right you can see this graphically, this is showing in one particular subject the sweat gland nerve fiber density seen with immunofluorescence staining using a green staying called PGP9.5. At the top we you see a baseline stain of a sweat gland in this patient where you see very faint PGP9.5 staining. At the bottom, we see that same patient at 24 months, the Patisiran therapy showing much more intense green PGP9.5 staining indicating an increase in sweat gland nerve fiber density in this patient.

So in summary, Patisiran was found to be generally well-tolerated in patients out to 25 months. There was sustained knockdown of TTR ranging from 80% to 93% over a 24-month period. There is preliminary evidence showing improvement in the neuropathy impairment score at 24 months with a mean 6.7 point decrease in the mNIS+7. And these results in total are consistent with the therapeutic hypothesis that Patisiran can potentially halt or improve neuropathy progression.

Turning to the APOLLO phase 3 study which is ongoing, slide 56 is now looking at the enrollment by country. A total of 225 patients with hATTR-PN have been enrolled from December 13 through January 2016. Patients were enrolled at 44 sites in 19 countries and the breakdown of that enrollment by country is shown in this pie chart.

Moving on to slide 57 and the baseline demographics for these 225 patients, the median age was 62 years. About half of these patients had a V30Met genotype, the other half a non-V30Met genotype. For those with non-V30Met, there were 57 different mutations represented. About half of the patients were FAP stage 1 and half FAP stage 2 and about half of these patients had previous tetramer stabilizer use. Patients were not allowed to stay on TTR tetramer stabilizers once they came onto the study so this reflects patients who had previously used tetramer stabilizers.

Additional baseline characteristics are shown on slide 58. The baseline mean NIS score was 59.3 indicating a fairly significant degree of neurologic impairment with a range of 6 to 141.6. Roughly half of these patients had cardiac involvement as defined as having a LV wall thickness of 13 millimeters or greater with no history of hypertension or aortic valve disease. And you can see that these patients with cardiac involvement had significant involvement with LV wall thickness averaging 1.7 and with substantial increase in NT-proBNP.

Slide 59 looks that the correlation between either the baseline mNIS+7 score or the baseline Norfolk quality of life and either FAP stage or PND score. And you can see that there was a very strong correlation between mNIS+7 and FAP stage between Norfolk quality of life in FAP stage and a similar correlation between mNIS+7 and Norfolk quality of life with a PND score. These data further highlight the fact that both mNIS+7 which is a primary endpoint on APOLLO and Norfolk quality of life which is the first secondary in point on APOLLO are clinically significant measures given the fact that they correlate so well with the disease stage and therefore the severity of disease at baseline.

So in summary, APOLLO is the largest controlled study of patients with hATTR-PN to date. It is globally representative; patient population comes from 19 countries and 44 sites. These patients with hATTR-PN who are enrolled on a study represent a wide range of TTR mutations in disease severity including a substantial proportion of patients with cardiac involvement which allows us to extend Patisiran's potential effects on other disease manifestations including cardiac manifestations. And as Eric noted earlier, the results from this key pivotal study are expected in mid-2017.

Finally, I'm going to move on to a preview of the Revusiran Phase 2 open label extension study, 12-month data. The study design is shown on slide 61. In this particular study, patients who had completed the Revusiran Phase 2 study were eligible to roll over onto the open label extension study. These patients initially received a loading dose of Revusiran which was a daily dose for five days followed by weekly doses administered for up to two years. A number of clinical endpoints were measured every six months on this study including measures such as 6-minute walk distance as well as other measures that are shown in the study objectives portion of this slide. In addition, serum TTR levels were measured serially and of course, safety was also followed closely in these patients.

Slide 62 shows the demographic and exposure. A total of 25 patients were enrolled onto this study, 14 with hATTR-CM and 11 with wild type hATTR. You can see that most of the patients in either of these subgroups had NYHA Class II or III disease. Notably the mean time from diagnosis to first dose on this study was almost three years and a minority of subjects on the study were receiving a concurrent tetramer stabilizer. At this point, patients have received treatment for a mean duration of close to 11 months.

Slide 63 is now looking at the characteristics of patients who either remain on study or who came off the study due to either death or disease progression. What we found here and what is shown in this table is that patients who came off study for death or disease progression had a substantial longer period of time from ATTR diagnosis to first dose on the study, that time being 48 months compared to 25 months for patients who remain on study, that difference was statistically significant.

It was also a difference in the baseline 6-minute walk distance, the 6-minute walk distance trended lower in patients who came off study for death or disease progression with a p-value that was approaching significant.

Slide 64 shows how this average time from diagnosis to first dose differs between the hATTR-CM in patients that are on the Phase 2 open label extension study and those hATTR-CM patients who are being enrolled into the Phase 3 ENDEAVOUR study which is ongoing. As you can see from this bar graph, the average time from diagnosis to first dose in the Phase 2 open label expansion study for these patients was close to 35 months compared to only 13 months in patients the first 139 patients enrolled onto the Endeavour trial suggesting that these patients enrolled onto the ENDEAVOUR study are somewhat earlier in the course of the disease and therefore potentially expect to see less in the way of dropouts due to disease progression or death in that study.

Slide 65 provides a review, a summary of safety from the Phase 2 open label extension study with the common adverse events seen in at least 20% a patient shown on the table on the left. Overall, 14 patients, 56% had serious adverse events but only one was deemed possibly related to study drug. This being a patient with lactic acidosis who discontinued treatment but you had multiple other comorbidities that were not considered to be related to study drug.

There were seven deaths in total all not considered related to study drug. Four patients discontinue treatment due to drug related adverse events; three of these patients were previously reported to have had discontinued due to injection site reactions or diffused rash. There were no new cases of discontinuation due to injection site reactions and rash and there was the one patient who discontinued due to lactic acidosis. The injection site reactions were reported in 48% of patients and the majority of these were mild in severity and there were no other notable changes in liver function tests, renal function or hematologic parameters including platelets.

And the next slide, slide 66, presents a similar graph as shown for Patisiran looking at whether there was any correlation between percentage or knockdown and the percent change in platelet count from baseline. As you can see, there was no significant decrease in platelet count in patients who followed on the study to date and there was no correlation seen between the degree of TTR knockdown and any modest change in platelet count.

Slide 67 looks at the pharmacodynamic data and as you can see in the top graph looking at all patients receiving Revusiran at a dose of 500 milligrams weekly, we have TTR knockdown data out as far as 18 months and you can see that there is rapid and robust lowering of TTR with a mean maximal knockdown of 88.4% and an individual maximum knockdown of 97.5% and you can see that this knockdown occurs early and is clamped out to 18 months.

The bottom graph looks at the wild type patients versus the hATTR-CM patients and we see essentially equivalent knockdown in these two subgroups.

Turning to slide 68 now and looking at the change in six-minute walk distance, again the hATTR-CM patients, we found overall that the results were in line with the natural history data that we have previously reported in the hATTR-CM patients. We saw that in five out of the nine evaluable hATTR-CM patients. We saw generally stable six-minute walk distance at 12 months compared to baseline with a mean change of minus 14 plus or minus 8 meters.

Finally on slide 69 looking at other clinical measures that were followed on the study and looking in particular at cardiac biomarkers, echocardiographic features of disease and cardiac MRI, we essentially saw little to no change from baseline at 12 months in either cardiac biomarkers or in wall thickness ejection fraction, LV mass or longitudinal stream.

So in summary on slide 70, the Phase 2 open label expansion study includes a patient population with advanced hATTR cardiac amyloidosis. The longer time from diagnosis was identified as a risk factor for discontinuation due to disease progression and death. The preliminary data from ENDEAVOUR suggest that patients have shorter time from diagnosis to first dose of study compared to the Phase 2 open label expansion study patients. We now have safety and tolerability for Revusiran out to 18 months of exposure.

We see durable knockdown of TTR by Revusiran out to 18 months and the six-minute walk data results are generally in line with natural history data with the majority of evaluable hATTR-CM patients showing stable six-minute walk distance at 12 months.

With that I will turn it back over to Eric.

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

Great. Thanks, Jerry. We can now open it up for questions. Again as a reminder if you have any questions on the webcast, please hit the button and send those in.

Jared, I think some general interest on the data we see from the Phase 2 OLE and how can that possibly have an impact on how we estimate the potential for success in APOLLO? In particular, given the mean NIS+7 scores are different between APOLLO and the OLE, do you think that has in the reason for concern, do think the patients will still do as well as the patients that have done apparently in Phase 2 OLE?

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

Well we think that while the Phase 2 open label expansion study patients had a mean baseline miss of approximately 35 compared to a mean baseline miss of approximately 55 in the APOLLO study, it is clear that the Phase 2 open label extension study patients have fairly advanced disease. And when we look at the change in mNIS+7 over a 24-month period, as I showed in one of the slides previously, you can see that regardless of where patients start -- so even patients with high mNIS+7 at baseline, mNIS+7 scores that are in the 120 to 125 range, those patients seem to derive the same benefit as patients with lower mNIS7 scores at baseline. And this is very encouraging to us because it suggests that the impact of TTR lowering can be seen really regardless of where patients start with regard to their baseline NIS or baseline mNIS+7 or essentially the fact that TTR lowering has the potential to impact patients regardless of their baseline disease severity.

So we think we are encouraged by those data from the Phase 2 of the label expansion study and I think they do both well for being able to see a similar impact across the full spectrum of disease in patients enrolled onto the APOLLO study.

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

Then tell me a little bit more about the nerve fiber density data and what do you think that might mean and how may that be correlated to any aspects of mNIS+7?

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

The nerve fiber density data are exciting to us because they potentially are showing the first evidence for nerve regeneration in response to TTR lowering. It was very interesting to us that we were able to see this increase in sweat gland nerve fiber density in the proximal leg first before we started to see it then in the distal leg and that was very consistent with what normally happens with neuropathy. Normally with a peripheral neuropathy, one starts to lose function in the distal part of an extremity first and then it moves up to the proximal part of the extremity.

When there is recovery, one tends to see recovery first more proximally and then more distally. So the fact that we are seeing an increase or improvement in (inaudible) nerve fiber density first more proximally and then later more distally is in line with that sort of biology. I think the fact that we are seeing this improvement in nerve fiber density along with seeing this improvement in mNIS+7 in a majority of patients is very encouraging to us. That TTR lowering may be having an impact on the natural history of the disease.

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

There is a question about on the Revusiran OLE study, we noted that five of the nine are generally stable six-minute walk distance. Have we talked publicly about any of the split between what those five patients look like, their demographics versus the four that didn't seem to be as stable?

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

We haven't yet looked on a patient by patient basis at whether there were differences in a baseline characteristics between those who remained stable versus those who were not stable. But as we noted with regard to patients who were not even able to stay on study long enough to have a 12 month evaluation, clearly time from diagnosis to going on to study was a poor prognostic factor for patients in terms of their ability to stay on long enough to achieve benefit of the drug. So for those patients who do appear to be stable at 12 months, we assume this is in part because they are able to stay on study long enough to hopefully drive some benefits from TTR lowering. And I think as we look -- we have further follow-up of these patients we will get a better sense for whether these patients remain stable over a longer period of time.

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

Given the discussion we have had earlier about the mix phenotype and how we seem to see more patients that have maybe primarily polyneuropathy but also some cardiac involvement, given the fairly large cardiac subgroup we have defined in Apollo, what do you think the potential is for the FDA to consider the cardiomyopathy type label for Patisiran?

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

Well, it is interesting to us that on the Phase 2 open label expansion study in addition to this improvement that we are seeing in mNIS+7, we saw a stabilization of a number of other clinical measures and in fact there is a cardiac subgroup of 11 patients within the Phase 2 open label expansion study where we did actually perform serial echocardiograms and cardiac biomarkers and were able to see in those particular patients stabilization of those various parameters.

So it appears that in this small population that the cardiac subgroup within the Phase 2 open label extension study TTR lowering maybe having an impact on the progression of cardiac disease in addition to having an impact on the progression of neuropathy. So we think on APOLLO the fact that half of these patients have substantial cardiac involvement does provide us with an opportunity to see whether TTR lowering also has an impact on those particular endpoints.

Now these are not primary or secondary endpoints on the APOLLO study. They are important exploratory endpoints but it is feasible that if we were to show an impact on these various cardiac parameters in the APOLLO study and they show a real difference between treated and placebo patients that could be taken into consideration by FDA with regard to the potential label claims.

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

And at a minimum we would engage the discussion to see if there is something that is appropriate.

There is a question here, in the Phase 2 Revusiran only, there appears to be a discrepancy between six-minute walk distance and BNP changes. How would you interpret that?

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

Well, the six-minute walk distance change and the BNP are really very different measures. The six-minute walk distance measure is the functional measure which is a very important kind of functional measure for these patients with cardiomyopathy and the reason why it is a core primary endpoint in the ENDEAVOUR study. BNP as a cardiac biomarker is a much more [labile] somewhat unstable biomarker that can be altered by changes in volume status, by changes in whether patients are fluid overloaded or not fluid overloaded can have a profound impact on the BNP. So we tend to see a lot more variability to BMP over time than we would in something like the six-minute walk distance.

So we really put much more emphasis I think on the six-minute walk distance data for this particular population I think it is more reflective of the cardiac function and it does appear to be a more reliable measure over time compared to something like the BNP.

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

There is a very specific question on the comparison of the safety profile between Patisiran and Revusiran and in particular it was noted for Patisiran, UTIs are noted in about 20% of patients with Patisiran but that was not noted on Revusiran. Do you have any insight to that? Is it that particular product or just small numbers in open label study?

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

I think once again that is important to note and I think I made this point when I was reviewing the Patisiran safety slide that in that table that is looking at adverse events, those are all adverse events whether or not they were related or unrelated to study drug. As it turns out there have been no urinary tract infections that have been deemed to be related to study drug in the Patisiran trial. And so I think when you see urinary tract infections on these studies, they are probably more related to autonomic dysfunction of the bladder that predisposes these patients to see urinary tract infection.

So because of these patients on the Phase 2 open label Patisiran study that have neuropathy, they are the ones who are likely to have autonomic dysfunction, bladder dysfunction and therefore are more likely to have urinary tract infections because of their disease whereas on the Revusiran study these patients have predominant cardiac involvement. They don't have the same autonomic dysfunction, they don't have the same bladder dysfunction so you won't see as many urinary tract infections in the Revusiran study just because you don't see as many of those infections in that particular form of the disease.

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

As noted obviously in the Revusiran study, the ENDEAVOUR patients have been -- seem to be earlier in their diagnosis. The question that comes on for both programs, do you think the best results could be linked to getting to patients sooner, treating the disease earlier? Do you think that would be beneficial?

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

I think it probably is a truism that probably early intervention is always best for patients but I think in terms of whether TTR lowering can have a clinically significant impact on the natural history of the disease, I think that the Patisiran data suggests that regardless of whether patients come in early or late that there is still the potential for a significant impact of TTR lowering.

In patients with cardiomyopathy, it is a somewhat different story because the cardiomyopathy moves much more rapidly and survival for these patients is much shorter than patients with a neuropathy. So for patients with cardiomyopathy who present late in their disease, there perhaps is not as much of an opportunity or as much time for those patients to derive benefit from treatment compared to patients with neuropathy who present in an advanced who still have a better survival than patients with cardiomyopathy.

So I think that there is a potential for patients both with cardiomyopathy and neuropathy to benefit from TTR lowering regardless of the disease severity but I think what we've seen so far with Patisiran in particular makes us particularly optimistic about being able to see an impact both in early and later stage disease.

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

Just a reminder to folks on the webcast, if you have questions please go ahead and submit those. We have time for one or two more.

Can you explain a little bit more the correlation data that was presented in the Phase 2 OLE for Patisiran?

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

The correlation data we think are very important because this was really the first time that we were able to show a real connection between the degree of TTR lowering that we are able to achieve with Patisiran in a given patient and the impact on the progression of their neuropathy where the deeper the TTR lowering, the greater the degree of TTR knockdown the more improvement we saw in the mNIS+7 score.

I think this is also an important finding because as noted, a number of patients on the Patisiran open label extension study are also on concurrent tetramer stabilizers. Now these TTR stabilizers of course have no impact on TTR levels. In fact if anything they have been shown to cause an increase in TTR levels by 25% to 30%. They certainly don't lower TTR levels.

The fact that within this study even in patients who are on tetramer stabilizers concurrently, the fact that we see this strong connection between TTR lowering and improvement in mNIS+7 really tells us that it is the effect of Patisiran and the effect on TTR that is having this impact on their neuropathy progression as opposed to any impact of the tetramer stabilizer itself.

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

And then maybe related to that then, any significance for why it shows that TTR knockdown at day 17?

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

The reason we chose day 17 was because these patients are on study for a two-year period and during that two-year period, sometimes patients can miss several doses or sometimes patients may even miss having a blood draw for a TTR level. And when you miss either several doses or you miss a blood draw, that can impact the measurement of your TTR burden over time and can therefore make showing a correlation more inaccurate and more difficult. We find that there is a very strong correlation between the day 17 TTR level and what is called the TTR area under the curve or the mean TTR knockdown over that 24 month period. Therefore it makes sense for us to use that very early time point which does correlate very strongly with TTR burden over time in order to show a correlation with mNIS+7 change over time.

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

I think we have -- it looks like one more question. How would you interpret the Phase 2 Revusiran data with and without imputation. And maybe broadening that slightly, how is the analysis being done in the Phase 2 OLE going to be the same or different in the ENDEAVOUR study?

Jared Gollob, Alnylam Pharmaceuticals, Inc. - VP, Clinical Research

I think the data from the Phase 2 open label extension study looking at imputation versus no imputation, looks fairly similar and the imputation done is for patients who are unable to perform the six-minute walk test or assigned a zero was essentially for the six-minute walk distance.

The ENDEAVOUR primary endpoint is somewhat different. The ENDEAVOUR primary endpoint is a co-primary endpoint of both six-minute walk distance as well as TTR lowering. It takes into account whether patients are alive or not at the time that they are going to have a six-minute walk, distance determination, in addition to actually taking into account the actual distance that they walked.

So the statistical approach to the primary, co-primary endpoint on ENDEAVOUR is not exactly the same as the way we would approach looking at the six-minute walk distance in the Phase 2 open label expansion study.

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

That is great. I think that is all the questions we have today. So again we want to thank very much Jared for walking through all the data. Thank Dr. Berk for giving us the overview of the disease and obviously his perspective as a clinician treating this disease every day. And especially to Christina for sharing her story.

That is all we have for the TTR portion. I will pass it over to Josh to conclude.

Josh Brodsky, Alnylam Pharmaceuticals, Inc. - Senior Manager of IR and Corporate Communications

Okay. Thank you, Eric. This concludes our RNAi Roundtable for today. The replay and slides will be posted on the Alnylam website later today at alnylam.com/roundtables and the transcript will follow shortly thereafter. You can also visit that page to view bios of this event's speakers.

We look forward to your participation on Monday, August 22 at 10:30 AM Eastern time as we discuss our fitusiran program in development for the treatment of hemophilia and rare bleeding disorders. And in the weeks that follow to discuss additional programs from Alnylam's pipeline of investigational RNAi therapeutics. For more details on these future roundtables, please visit www.alnylam.com/roundtables.

Thanks everyone and have a great day.
