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Alnylam Pharmaceuticals, Inc. (ALNY)

Investor Meeting - Patisiran & Vutrisiran, for the Treatment of Transthyretin-Mediated Amyloidosis

CORPORATE PARTICIPANTS

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

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

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

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

MANAGEMENT DISCUSSION SECTION

Operator: Good day and welcome to the RNAi Roundtable. Today's conference is being recorded. At this time, I would like to turn the conference over to Josh Brodsky, Director of Investor Relations and Corporate Communications. Please go ahead.

Joshua Brodsky

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

Good afternoon, everyone. Thank you for joining us for today's RNAi roundtable where we'll be discussing patisiran and vutrisiran, RNAi therapeutics in development for the treatment of ATTR amyloidosis. I'm Josh Brodsky, Director of Investor Relations and Corporate Communications at Alnylam. With me today are Eric Green, Senior Vice President and General Manager of the TTR program; Mike, a patient living with hereditary ATTR amyloidosis; John Vest, Executive Director of Clinical Research; and Rena Denoncourt, Senior Director and Program Leader for vutrisiran.

Today's RNAi roundtable is the first in a series of roundtables that we'll be hosting over the next few months to review progress across our various programs. Today's event is expected to run between 60 and 75 minutes. Eric will moderate the Q&A session at the conclusion of the presentations. If you'd like to submit a question, you can do so at any time during the event by typing your question into the Ask a Question Field. Finally, as a reminder, we will be making forward-looking statements during the presentation and we encourage you to read our most recent SEC filings for a more complete discussion of risk factors.

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

Eric Green

VP & General Manager-TTR Program, Alnylam Pharmaceuticals, Inc.

Good. Thank you, Josh, and thanks, everyone, for joining us today to hear about our TTR programs. 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, harnesses a natural and catalytic mechanism. Through Alnylam's efforts, RNAi is a clinically proven approach that is currently being applied to two agents in the TTR space. One approved product, ONPATTRO, and one investigational agent, vutrisiran.

Alnylam has a substantial pipeline of products targeting different liver-expressed protein. To date, we have demonstrated human proof-of-concept with eight products and we have five programs in late-stage development.

One, actively under regulatory review and one, ONPATTRO, has recently hit its one year anniversary of commercial availability in both the U.S. and in Europe. Earlier this year, the positive Phase 3 data with givosiran and the recently announced positive Phase 3 data with inclisiran, further support our conviction for the future potential of RNAi therapeutics in both orphan indications and in diseases with larger [ph] patient (00:02:57) populations.

Today, we will focus on our TTR program, including commercial highlights for ONPATTRO, additional clinical development activities for patisiran, and the clinical development plan for vutrisiran. We are also pleased that one of our patient ambassadors has joined us today to share his story about living with hATTR amyloidosis.

Amyloidosis is a rare progressively debilitating disease caused by misfolded TTR proteins that accumulate as amyloid deposits in multiple tissues, including heart, nerves and the GI tract. Both hereditary and wild-type forms of this disease may present in adults with multi-system involvement and a high burden of disease is often fatal.

As we shift to talk about ONPATTRO in a few slides, it is important to note that ONPATTRO is currently approved for the treatment of the hereditary form of the disease in adults with polyneuropathy, with specific indications and limitations that vary by country or by region. Early diagnosis of ATTR amyloidosis is critical given the rapidly progressive nature of the disease. The range of disease manifestations may include a decline in cardiac function, impaired physical function and a progressive polyneuropathy, which result in pain, motor weakness and/or autonomic dysfunction, such as orthostatic hypotension and severe gastrointestinal distress. Typically, more than one or two of these symptoms will be present in each individual patient.

Diagnostic tools most commonly utilized today, shown here in the right, allow for a comprehensive assessment of a patient to enable the identification of the multi-system manifestations of the disease. Physicians may use both non-confirmatory and confirmatory diagnostic test to establish the differential diagnosis. Utilization of the various diagnostic tools upon initial suspicion of ATTR amyloidosis is becoming increasingly common in the importance of early diagnosis and early therapeutic intervention to support the best possible outcome for patients.

Our team remains committed to addressing the challenge of raising awareness of the disease and improving diagnosis of ATTR amyloidosis. Improved medical education and diagnosis will help patients reach treatment options faster. Again, the data are clear that when patients receive treatment earlier in their disease course, it improves their overall prognosis.

Our Alnylam Act program, available in the U.S. and Canada, has a free third-party genetic screen initiatives aimed at facilitating diagnosis of patients suspected of having hATTR amyloidosis. As of July, over 15,000 samples have been submitted to our partner Invitae and over 1,000 patients with pathogenic mutations have been identified, with a sustained

hit rate of 6% to 8% in the program.

Since there are other sponsored genetic testing programs available and HCPs are also able to use their own reimbursed genetic tests, this represents only a portion of the genetic testing volume in patients where hATTR amyloidosis is suspected.

We're also pleased to collaborate with 23andMe, a leader in direct-to-consumer genetic testing. Through our collaboration, all eligible 23andMe customers in the U.S. and select European countries who opt in to the Hereditary Amyloidosis TTR-Related Genetic Health Risk Report are notified if they are a carrier of a V122I,

V30M or T60A mutation, the three most common TTR variants in the U.S., and they therefore can receive more information about hATTR amyloidosis.

23andMe launched the Health Risk Report in April of this year and, a couple months later in July, we announced a jointly branded program in the U.S., the +myFamily program, to offer free [ph] Health + Ancestry (00:07:06) kits to first degree family members of 23andMe customers with a TTR variant. Since it started in mid-July, over 500 kits have already been supplied in this program. Through this collaboration, Alnylam is working to increase awareness of hATTR amyloidosis to support patients as they become more informed about genetic markers that may influence their health, and to reinforce our longstanding commitment to hATTR amyloidosis community.

Going back to the underlying cause of ATTR amyloidosis, namely the buildup of TTR amyloid in [ph] variance (00:07:45) tissues, it is important to remember that it all starts with the production of mutant and wild-type TTR protein in the liver. For many years, we have held the therapeutic hypothesis shown here that an RNAi therapeutic explicitly designed to target both mutant and wild-type TTR mRNA will reduce circulating TTR protein and prevent further amyloid deposits or clear existing deposits from the tissue. This would then lead to halting or improvement of the progressive manifestations of the disease in patients with hATTR amyloidosis.

I will now pivot from the disease of ATTR amyloidosis and begin discussing ONPATTRO. With ONPATTRO's approval in the U.S. in August of 2018 for the treatment of the polyneuropathy of hereditary transthyretin amyloidosis in adults, it became the first-ever RNAi therapeutic to be approved heralding the arrival of an entirely new class of medicines.

On this next slide, you can see the current regulatory approvals and associated indication statements for ONPATTRO around the globe. Our most recent milestone comes from Japan where just last week ONPATTRO became commercially available following the regulatory approval in June of 2019. I'm happy to announce that the first patients in Japan have already received their infusions of commercial ONPATTRO and we expect Japan to be a significant market for ONPATTRO over the coming years. Marketing Authorization Applications are currently under review in Switzerland and Israel and we anticipate a New Drug Application submission in Brazil by the end of this year.

We continue to expect continuous growth on ONPATTRO to come from three areas; finding and treating new patients in the existing markets, opening new markets through regulatory approval and/or pricing and reimbursement, and as a result of continued evidence generation efforts, highlighting the differentiated [ph] features (00:09:42) of ONPATTRO.

As we think about the total market opportunity for RNAi therapeutics in ATTR amyloidosis, the first step for ONPATTRO is within the hereditary patient population, specifically in patients with polyneuropathy, including those that may have a mixed phenotype, that is have both polyneuropathy and cardiomyopathy. As with most rare diseases, the true prevalence is difficult to know but we estimate that 20,000 to 30,000 patients worldwide would fall within the current ONPATTRO labels, again, noting that every country or region may have a different indication instead of data in the label. As we said previously, with more companies in the ATTR amyloidosis market, we believe overall awareness of this disease will continue to accelerate and we are enthusiastic about the benefit this will confer to patients.

The global success of ONPATTRO begins with efficacy and safety demonstrated in the APOLLO study in ATTR patients with polyneuropathy, providing a strongly competitive product profile, supported by a comprehensive commitment to medical and commercial excellence and operational execution.

Our commercial and medical affairs organizations have been built with a focus on physician education, patient advocacy and engagement and a robust offering of patient services. By applying the same innovative spirit to our commercialization activities as we have for years in our research and development efforts, our proactive approach to supporting patient access will also drive ONPATTRO's success.

We shared our global brand campaign [ph] imagery (00:11:24) before noting the reversal in neuropathy impairment from baseline as measured by the modified Neuropathy Impairment Score + 7, or the mNIS+, score in APOLLO, as well as a consistent positive impact on the other endpoints in the study.

It is important to note that infusion-related reactions have been observed in patients treated with ONPATTRO, and due to the role of TTR in vitamin A transport, there is a potential for vitamin A deficiency. The full safety information, one must review the product label for the relevant country.

Reviewing ONPATTRO's commercial performance in the second quarter, which we first announced in early August, we achieved $38.2 million in global ONPATTRO net product revenues in second quarter, with $10 million coming from the EU and $28.2 million coming from the U.S. And as of June 30, over 500 patients worldwide were receiving commercial ONPATTRO treatment. We're pleased with the overall growth and continued global demand this quarter even with increasing product options from recent market entrants and the availability of investigational drugs through Expanded Access Programs in clinical trials. Patients either in our Expanded Access named patient for similar programs, or those patients who are known to site at the time of ONPATTRO approval, were reached in the first couple of quarters of launch and we are now very much focused on reaching the de novo patient pool.

We believe that we are on track to have approximately 1,000 patients on patisiran across commercial, clinical studies and named patient or other reimbursed Managed Access Programs by year-end 2019, an exciting milestone in our overall efforts.

On the physician front in the U.S., in Q2, we saw continued growth both in the numbers of new prescribers as well as repeat prescribers. Over 50% of U.S. Start Forms received in the second quarter came from new prescribers. We believe new prescribers will continue to increase as HCP disease awareness grows fueled by multiple players engaged in disease state education. Regarding the mix of prescribers, in the second quarter, we continue to see about 50% of U.S. Start Forms come from cardiologists, which we believe indicates strong recognition of the need to treat the polyneuropathy of hATTR amyloidosis including in mixed phenotype patients.

Regarding U.S. market access as reported by external coverage reports, we're very pleased that we now have confirmed access to ONPATTRO, if prescribed, for more than 98% of U.S. lives across commercial, Medicare, Medicaid and other government payer categories. We're proud of this result in a very complex U.S. market access environment and believe that [indiscernible] (00:14:13) constructive, collaborative and proactive approach we've adopted with the payer community.

Turning to the EU and more broadly our Canada, Europe, Middle East and Africa regions, which we refer to as CEMEA, we're very pleased with ONPATTRO performance in the region. Some notable achievements in the second quarter included favorable and competitively differentiating technology assessments in Germany, France and Italy.

A highlight for the recent period was achievement of the pricing agreements with NICE in England and with pricing authorities in Scotland. We also received marketing authorization approval in Canada where ONPATTRO is now available for commercial use. Given the timing of pricing and reimbursement discussions in CEMEA, we

expect continued market access based growth in the number of commercial ONPATTRO patients for the rest of 2019 and into 2020. In addition to growth coming from patient finding and utilization when patients may experience inadequate responses, disease progression or tolerability issue with other agents.

Alnylam is committed to making the therapy that we redevelop available to the patients who may benefit from them. In this spirit, and to hold ourselves accountable to delivering on this commitment, we introduced our Patient Access Philosophy back in 2017. Last week, we released the first report with detailed metrics on a number of key parameters related to various aspects of patient access.

Notably, to-date, we've proactively engaged payers, who cover the vast majority of lives in the U.S., and successfully implemented value-based agreements with more than 10 commercial payers. They've also established programs and services to support patients being treated with ONPATTRO, including with financial and logistical aspects of ONPATTRO administration. Approximately 80% of U.S. patients have zero commercial co-pay for ONPATTRO.

We also remain committed to [indiscernible] (00:16:10) growing Alnylam to continued innovation and by delivering genuine value to patients and the healthcare system, not through arbitrary price increases. Our full 2019 Patient Access Philosophy Report is available on our website at news.alnylam.com.

So to further understand the perspective of a patient with ATTR amyloidosis and perhaps to make some of what we've been talking about a little more meaningful, I'd now like to introduce today's guest speaker. Mike participates in Alnylam's Patient Ambassador Program and he will be sharing his experience as an ATTR amyloidosis patient with polyneuropathy on commercial ONPATTRO.

Thank you for joining us today, Mike. Over to you.

Unverified Participant

Thank you, Eric. I grew up in a New Jersey suburb. I was a teenager in the late 1980s. It was my dad, my mom, my sister and me at home. Some evenings my dad would ask me if I wanted to tag along with him to work the next day, and I was always happy to go. I really couldn't imagine a more exciting way to spend my time. My dad didn't just shuffle papers at work. He was a police officer and detective in one of the most dangerous cities in America at the time. My name is Mike, and I'd like to thank Alnylam Pharmaceuticals for sponsoring me to share my story of living with hereditary ATTR amyloidosis.

The violent crime rate in the city where my dad worked was more than double that of national average, which really kept my dad busy. And as a teenage boy, I found it really exciting. I had the opportunity to see some real eye-opening sites. I remember once my dad had taken me down to what they call the cell block, which was like a prison, and we walked through where all the inmates were. They were inside their cells of course, but I heard words I had never heard before, and some of them threw things at us through the iron bars. But even in situations like that, I was never afraid because my dad was with me. He was respected and trusted by his fellow officers in blue. And he would spend more than 30 years on the force collectively all in New Jersey.

While growing up, I love to play basketball. I played basketball everyday if I could. I was on the high school team and would even earn some extra cash playing two on two with my high school teammate. We put some cash under the basket and then play challengers for it. One time, we'd beat our opponents for two total strangers and

one of them wasn't having it and pulled a gun on us. My friend ran but I talked the guy down. And I'd like to think that something my dad would have done as well. But after that experience, my friend and I stuck to our home court.

When I was a sophomore in college, I remember my dad telling me that he wasn't feeling well. He would get pains in his wrists and he was having difficulty walking up the stairs. This was the start of what we now understand as our family's journey with hATTR amyloidosis. My dad experienced symptoms of bilateral carpal tunnel syndrome, systemic polyneuropathy with numbness and tingling in his extremities, all starting in 1996. My family and I searched for answers across the country and visited all kind of specialists. At one point, my dad was diagnosed with ALS, or Lou Gehrig's disease. That was in 2001. But the treatments given to him for that just made him worse.

Dad eventually retired from the police force due to his decline in health. And it was really hard to see, hard to accept that my hero of a dad, who'd I had always felt was invincible, now had to use a walker to get around.

Finally, we received my dad's diagnosis in late 2005. It was what the doctors had called hATTR amyloidosis with the gene mutation of P64L. We had no clue what that meant. But I had recently graduated university with a Biology and Chemistry degree. So I started doing some research and learned there were no treatment options for hATTR amyloidosis available at the time other than a liver transplant.

My sister and I knew we should be tested, because hATTR amyloidosis was an autosomal dominant genetic trait and it could be passed down. She was married at the time with no children and she tested negative. I was married with three children, but I decided to wait to be tested. Other than liver transplants, there were no options for hATTR amyloidosis available at the time. So, I didn't see the point. Some people test positive, but never developed any symptoms. I thought if I were to test positive, I'd be constantly haunted by every stomachache, every stubbed toe, and I didn't want that. I wanted to focus on living my life. I didn't want to be stressed. I wanted to be blessed.

Because my dad's diagnosis had come later in his disease progression, he never got on the liver transplant list. Before the end, he had progressed from a wheelchair to being bedridden. The quality of his life was so poor. He hung on a few more years and ultimately passed away in 2013 at the age of 67. Through it all, my mom was his number one supporter and loving caregiver. But this was a really hard time for me and my family. But we supported each other through it as best we could. We'd need each other in the years to come too because dad's story had ended but mine was just beginning.

A few years ago, in August 2016, I started having pain in my wrists and hands and numbness in my fingers and toes. My heart sank. I immediately looked for a nearby amyloidosis center so I can go in and request genetic testing. I was afraid. I kept thinking about my family and wondering what they do if I was diagnosed with hATTR amyloidosis. I had seen my dad waste away to nothing and now I was having the same symptoms he'd had. What will my wife do, I thought, how would she take care of our beautiful children? She was a stay at home mom raising three kids and I worried about her paying the bills if I was out of the picture. Then I remember what the key to having a chance with this disease was, it's early diagnosis.

I underwent testing as soon as possible and then did some extra reading on hATTR amyloidosis as I awaited my test results. Two or three months passed and I was experiencing symptoms that made it increasingly difficult to sleep, play with my kids and enjoy life in my 40s. I remember looking at my hands and seeing my dad's hands with the atrophy on my palms. I had odd pains in my hands and arms and my lower legs would go numb at night.

My feet were always as cold as ice. I even had horrible dreams and visions of my dad lying in bed wasting away. Sometimes I dream that it was me.

I found it difficult to focus at work and remain optimistic. So I use this time to grow in my faith. I needed the strength and prayers of my church family to get me through this time. That October, my family and I went on a road trip to my undergraduate school for alumni weekend with our best friends. We had just pulled into a rest stop to get some coffee for everyone when my cell phone rang. I saw the number displayed was from the center where I had gone for genetic testing. So I told everyone to go in and I would meet them inside. But I never joined them that day.

I answered the phone and the nurse on the line asked me to come and meet the doctor the next morning. I think I was actually a little rude to her that day and I said, I'm out of state for the weekend but I think I know what this is about, how about you put the doctor on the line. She did, he picked up and I learned that my test results had come back gene positive for hATTR amyloidosis, the same gene mutation my father had.

It was like a big punch in the stomach. I hung up, then broke down in tears as I sat in the driver's seat of our minivan waiting for my family and dear friends to finish their coffee. All the years that I saw my dad struggle and deteriorate in health, came flashing back to me. My wife knew what had happened as soon as she saw my face. The two of us cried quietly, as we continued our drive to Alumni Weekend with our kids sitting unaware in the back seat.

Once we got to our hotel, my wife and I told our children about the diagnosis and the conversation was very emotional. They remembered my dad and knew he had passed from this disease. And it was a difficult weekend but I was glad that I was with my family and friends through it all.

When we returned home, my wife and I went in to see the physician who provided us with the test results and tried to determine our next steps. I had spent months studying what my options for hATTR amyloidosis would be, so I felt well prepared. The doctor said I was a candidate for a liver transplant, as I was young and relatively healthy. However, I told him I heard of a clinical study with an investigational medicine called patisiran that I was interested in. But he said patisiran wasn't available locally yet. He hoped that their center might be part of Alnylam's Expanded Access Program in a few months. This would allow me to get access to treatment outside of a clinical trial and prior to FDA approval, if I qualified.

I knew what my dad had gone through and that as this disease progresses, it takes more and more of your abilities. I asked to be contacted when the EAP was available and my wife and I left the center feeling bleak. Some time went by and I kept calling the center to see if they'd gotten set up, but they were moving slowly. I decided then to be my own advocate. I couldn't afford to lose any more time. At the time, the EAP was only being offered in two locations in the United States, one in Iowa and one in Boston. I was willing to go to Boston. So I contacted the site. Within weeks, I scheduled my first infusion with patisiran. I was so excited by how everything came together. Sometime later, the FDA approved ONPATTRO for the polyneuropathy of hATTR amyloidosis in adults.

ONPATTRO is given as an IV infusion every three weeks. So I needed to adjust to having this done on a regular basis. Since ONPATTRO can cause confusion-related reactions, I receive medicines at least 60 minutes before each ONPATTRO infusion to help me lower my chance of this happening. My doctor also asked me to take a vitamin A supplement every day since ONPATTRO can lower the amount of vitamin A in your blood, which can affect vision.

Together, my doctor and I discuss the most common side effects of ONPATTRO, which are respiratory infections such as colds, sinus infections, and nasal congestion. I made the decision to continue with the commercial drug after the EAP. I have found Alnylam Assist, Alnylam's Patient support program for patients prescribed ONPATTRO, to be very helpful, while navigating the complex network of medical professionals and insurance. And I have now switched from my infusion facility in Boston to my new one in Philly. When I was first diagnosed, I was very active in support groups trying to help others. Over the course of this time, I have met and discussed hATTR amyloidosis with so many wonderful people, patients, caregivers, and loved ones.

My kids still haven't been tested. Our genetic counselor advised us to wait until they can make the decision for themselves when they get older. My kids know the disease that I have, and that it's autosomal dominant. And hearing that from children is a bit odd sometimes. My son, who's a teenager, he's my emotional guy. He'll look at me and ask, will I get the disease? And I tell him the truth, and say, we don't know. But what I do know is that there are treatment options available now that didn't exist when grandpa was alive. You don't need to worry about it unless you have symptoms. And then, we laugh and tell each other to watch out for all the other things that you can die from like questionable food choices and things like that.

I'm happy to report that my symptoms have improved since I started on ONPATTRO. I no longer have pains in my hands and feet, and the numbness and tingling only happen at night in my hands. Whereas, it used to happen all over and all the time. At least, this has been my experience. And it's important for patients to speak with their doctor about whether ONPATTRO is right for them. Mentally, I've accepted that I need to have an infusion every three weeks, just like clockwork. It doesn't upset me. I just know this is something I have to do.

With permission from my doctor, I continue to work full time. I work in pharmaceutical research and development, and teach graduate courses in pharmaceutical management. My wife and I travel frequently, we went to South America recently. My work is really flexible and I've been able to use family medical leave time to work my infusions into my schedule. My family is thriving. All three of our kids are in scouting, play sports, and are involved in church activities. My daughter is a year-round swimmer and both my sons play baseball and basketball. We love to play ball in the backyard and in the driveway together.

I miss my dad all the time. And I can't help thinking that if ONPATTRO were available back when he was diagnosed, he and his doctor may have chosen this treatment for his polyneuropathy symptoms. But above all, I'm so thankful to be able to concentrate on the good things in my life, like spending time with my wife and being a loving dad to my kids. Thank you.

Eric Green

VP & General Manager-TTR Program, Alnylam Pharmaceuticals, Inc.

Thank you so much, Mike. We really appreciate [ph] you taking (00:33:00) the time today to share your story with us. We have a couple of questions coming in on the webcast. But we're going to hold those until the end of the presentation, as Josh mentioned.

We will now pivot to the continued development of patisiran in ATTR amyloidosis. I would like to introduce Dr. John Vest, an Executive Director in our Clinical Research group. John will review some data we've recently presented, as well as discuss our efforts to generate additional data in new patient segments to continue patisiran clinical development. John?

John Vest

Executive Director, Clinical Research, Alnylam Pharmaceuticals, Inc.

Thank you, Eric, and hello, everyone. My name is John Vest, and I'm the clinical lead for our TTR programs. At the Peripheral Nerve Society Meeting in June, new results were presented from the ongoing Global Open-Label Extension study, or OLE, of patisiran that showed a sustained improvement in neuropathy impairment and quality of life for patients after at least 30 months of treatment with patisiran. Recall that the patient population in the Global OLE study comprises patients who were previously in the APOLLO Phase 3 study, both the patisiran arm and placebo arm, as well as those who were previously in the Phase 2 Open-Label Extension study.

As shown here, patients who received patisiran for 30 to 36 months demonstrated sustained improvement in neuropathy impairment and quality of life relative to the corresponding parent study baselines, as indicated by mean negative changes compared to baseline in mNIS+7 and Norfolk Quality of Life scores, respectively. These are the blue and dark purple curves that can be seen in each figure.

Furthermore, the rapid trajectory of disease progression among APOLLO placebo patients that occurred during the parent study, the light purple line, was halted and, in a majority of patients, reversed once patisiran treatment was initiated in the Global OLE. Nevertheless, placebo patients did not return to their parent study baseline, as measured by mNIS+7 or Quality of Life scores due to the disease worsening experienced whole on placebo and APOLLO. This highlights the importance of treating patients as early as possible to minimize the advancement of disease.

Importantly, with this additional year of treatment with patisiran, the safety profile remained acceptable and consistent with previous studies. Thus, patisiran continues to show a positive benefit-risk profile.

Also at PNS, an analysis of the subset of APOLLO patients who discontinued tafamidis prior to study entry was presented. A little over half of the patients in APOLLO had prior stabilizer use before entry to the study, with one-third of the total patients previously on tafamidis, most of whom discontinued tafamidis due to disease progression. Patients with prior tafamidis use who received patisiran in the APOLLO experienced significant improvement from baseline in polyneuropathy and quality of life compared with placebo, as shown in the two figures, and performed very similarly to the overall population in the study. Safety and tolerability in the prior tafamidis group was consistent with that seen in the overall APOLLO population.

Just two weeks ago in Berlin, at the Second European Meeting of the ATTR Amyloidosis for Doctors and Patients, we presented results from two different projects. The first results on the left are from a comprehensive proteome-wide biomarker analysis of samples from the APOLLO study. This analysis was conducted to interrogate system-wide changes in the proteome in response to treatment and to identify potential biomarkers for early detection of disease. Notably, to our knowledge, this biomarker study represents the most comprehensive plasma proteomics analysis in patients with hATTR amyloidosis performed to date, and the first system-wide proteomics interrogation of response to an RNAi therapeutic in humans.

Across greater than 1,000 proteins screened, a significant change was observed in the levels of 66 proteins following patisiran treatment in APOLLO. We identified a protein called neurofilament light chain, or NfL, a well-described biomarker of neuroaxonal damage that was shown to have the greatest statistical significance for change relative to placebo over the 18-month study period. A correlation between the changes in NfL levels and polyneuropathy, as determined by the mNIS+7 score, indicated that decreasing levels of NfL are associated with improvements in measures of polyneuropathy.

In our view, these data support further evaluation of NfL as a potential biomarker for ATTR (sic) [hATTR] (00:38:22) amyloidosis that may facilitate earlier diagnosis of polyneuropathy and may enable monitoring of disease progression and/or regression over time, with or without treatment. Moreover upon further evaluation, NfL may also offer an easy and convenient blood test to detect polyneuropathy in patients with mutations that have historically been thought to predominantly cause cardiomyopathy – for example, V122I – but where underlying nerve damage often occurs and can be overlooked.

At the same meeting, we also presented results of an analysis from the UK Biobank characterizing the association of the T119M genotype with mortality and vascular disease as shown on the right. The T119M variant encodes a thermodynamically and kinetically stabilized TTR protein that increases the stability of wild-type and mutant TTR tetramers by slower tetramer dissociation, a mechanism that establish the therapeutic rationale for small-molecule TTR tetramer stabilizers. People with T119M variant have higher plasma levels of TTR.

A previous Scandinavian study of over 68,000 subjects and 321 carriers found an association of the T119M variant with extended lifespan and reduced vascular disease. However, following on from this observation, we investigated the potential effect of the T119M TTR variant on vascular disease and mortality in a much larger cohort from the UK Biobank, representing over 330,000 subjects and over 2,500 carriers of the variant. The analysis showed that carriers of the TTR T119M variant were not protected against vascular, cardiovascular, or cerebrovascular disease, or death. Furthermore, no difference was seen between T119M carriers and non-carriers in their time to death following a diagnosis of vascular disease. These findings suggest that stabilization of the TTR tetramer and/or higher plasma levels of TTR do not confer protection against vascular disease or death in a general population setting.

Moving on to the next slide, late last week at the Heart Failure Society of America Meeting in Philadelphia, we presented data on the presence of polyneuropathy signs and symptoms among patients with hATTR amyloidosis with confirmed cardiomyopathy. These data demonstrate that among these 206 patients with confirmed cardiomyopathy, over half had signs and symptoms of polyneuropathy based on clinical evaluation and analysis of medical history. Importantly, medical history of neuropathy tended to precede or coincide with signs and symptoms of cardiomyopathy, even in V122I patients traditionally thought of as a predominant cardiac phenotype. In our view, these data suggest that polyneuropathy maybe an early sign that is potentially overlooked in patients with hATTR amyloidosis, and underscore the importance of multisystem disease assessment to identify and fully characterize patients prior to them accumulating greater disease burden.

Also at the HFSA meeting, we presented new results from a phenome-wide association study, or PheWAS analysis, of the UK Biobank demonstrating a significant association of the V122I mutation, a highly prevalent mutation in the TTR gene that has historically been associated with a predominantly cardiac phenotype with a clinical diagnosis of polyneuropathy. Among a subpopulation of over 6,000 unrelated black participants, 243 subjects – with the mean age of 52.6 years – were carriers of the V122I mutation, equating to an allele frequency of 2%. Among the carriers, polyneuropathy was significantly associated with the V122I genotype. The significant association of V122I with polyneuropathy was further replicated in the Penn Medicine Biobank from over 5,700 black participants with 190 subjects who were V122I carriers.

In addition, there was nominally significant evidence that carriers of V122I were in increased risk for other signs and symptoms of hATTR amyloidosis, including carpal tunnel syndrome and urinary retention. Interestingly, in this analysis, there was no association of V122I with cardiomyopathy, likely due to the younger age of the carriers in the UK Biobank at the time of analysis, as compared to the age at which cardiomyopathy symptoms of hATTR amyloidosis typically present, which is the literature is more than 65 years of age. Overall, these findings demonstrate an association of V122I with the presence of a mixed clinical phenotype, supporting the need for a

broad assessment of a patient's overall health to look for multisystem manifestations of hereditary ATTR amyloidosis, which often include both cardiomyopathy and polyneuropathy.

Finally, at HFSA, we presented data on baseline disease characteristics in patients enrolled in APOLLO and the Global OLE studies to identify risk factors for mortality in patients with hATTR amyloidosis with polyneuropathy. Based on [ph] mean variate (00:44:32) and multivariate Cox proportional hazard analyses, elevated NT-proBNP, severity of neuropathy, and non-Val30Met genotype were identified as the three most significant risk factors for mortality in this patient population. In the APOLLO population, at baseline, the proportion of patients with risk factors of both elevated NT-proBNP and non-V30M genotype was higher in the patisiran arm compared to placebo.

Overall, the exposure-adjusted mortality rates from the integrated experience of all patisiran-treated patients from the Phase 2 OLE, APOLLO, and the Global OLE was 4.8 per 100 patient years, which is at the lower-end of the expected range for patients with ATTR amyloidosis. A further note, mortality rates per 100 patient years were highest in patients from the APOLLO placebo group, whose disease had advanced during APOLLO; and lowest in patients from the Phase 2 OLE patisiran group who were treated the earliest in their disease.

Finally, exposure-adjusted mortality rates were summarized by treatment arm and by subgroup defined by the combination of genotype and the other key risk factor, the NT-proBNP. For the highest risk factor profile that is non-V30M genotype and elevated NT-proBNP greater than 3,000 ng/L, the exposure-adjusted all-cause mortality rate per 100 patient years was lower in the patisiran group, 30.4, compared to the placebo group at 57.8. Furthermore, among patients with these risk factors, exposure-adjusted cardiac mortality rates per 100 patient years were comparable between treatment arms. From our perspective, these data further highlight the importance of earlier clinical suspicion and diagnosis of hATTR amyloidosis to enable treatment as early as possible in the disease course. For additional details on any of these recent presentations, please visit our Capella website to see the full posters.

Now, moving on to slide 30. While the APOLLO Phase 3 study enrolled patients with symptomatic neuropathy, we did generate important exploratory evidence for a potential beneficial effect of patisiran on cardiac manifestations of hATTR amyloidosis, as summarized here. [ph] We've (00:47:17) prospectively identified exploratory endpoints in a subpopulation of patients with pre-specified evidence of cardiac involvement, which comprised 56% of the overall study population, we showed a nominally statistically significant reduction compared to placebo in the cardiac biomarker NT-proBNP and the improvement in key echocardiographic measures of cardiac structure and function, as well as an improvement in functional status as measured by the 10-meter walk time. We also showed in a post hoc analysis of safety data from the overall study population, an approximately 50% improvement in mortality and hospitalization. A similar improvement was also seen for mortality in cardiovascular hospitalization. And from a safety perspective, we were heartened by the acceptable safety data we saw in the cardiac subpopulation as well as the entire population of the study.

These very encouraging data in cardiomyopathy have led us to gain alignment with the FDA on a new Phase 3 study we are calling APOLLO-B. We are very pleased to announce this morning that we have now initiated this study, which is a randomized, double-blind, placebo-controlled study of patisiran with six-minute walk distance as the primary endpoint after 12 months of treatment. We're going to study about 300 patients with either wild-type or hereditary ATTR amyloidosis with cardiomyopathy, and we are going to include patients who are either naïve to TTR stabilizers or who are progressing while receiving TTR stabilizers. We're excited to be starting up the APOLLO-B study and look forward to working with our physician partners to enroll the study.

Eric Green

VP & General Manager-TTR Program, Alnylam Pharmaceuticals, Inc.

Thank you, John. A lot of interesting new analyses and findings that was presented in the last few months. I would now like to hand over to Rena to introduce the vutrisiran update.

Rena Denoncourt

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

Thank you, Eric. Hello, my name is Rena Denoncourt, and I'm the Program Leader for our Alnylam's vutrisiran program and development for the treatment of ATTR amyloidosis. Alnylam has been and continues to be deeply committed to bringing innovation to patients with ATTR amyloidosis. I'm very pleased to share updates on our vutrisiran program with you today. Vutrisiran is an investigational RNAi therapeutic and the key component of our TTR portfolio.

Like patisiran, vutrisiran also targets TTR mRNA to suppress the production of both mutant and wild-type TTR protein. Vutrisiran utilizes Alnylam's enhanced stabilization chemistry and the GalNAc ligand to enable targeted delivery to the liver. It is administered as a low volume subcutaneous injection once every three months.

Vutrisiran has a clinical development plan that has been designed to be streamlined and efficient building on the years of work with key opinion leaders and regulators and our experience with patisiran. We have gained alignment on the Phase 3 study designs with regulators and major markets around the world. We completed a Phase 1 study in healthy volunteers, and I will review that in a moment.

Currently, we are executing on a robust Phase 3 program which includes two pivotal studies called HELIOS-A and HELIOS-B. Importantly, this pair of studies is aimed at assessing the potential of vutrisiran to treat the full range of multisystem manifestations of ATTR amyloidosis as well as the potential to treat the entirety of the ATTR amyloidosis patient population that is both hereditary and wild-type patient.

The Phase 3 clinical development program, which John will review in more detail, includes the HELIOS-A study and hATTR amyloidosis patients with polyneuropathy, which is now recruiting around the world, and the HELIOS-B study and ATTR amyloidosis patients which is anticipated to initiate by the end of this year.

The vutrisiran Phase 1 study included 80 healthy volunteers to receive a single dose of vutrisiran or placebo. As you can see, vutrisiran achieved robust and durable serum TTR knockdown. The TTR knockdown was potent and sustained in a matter that supports a quarterly dosing regimen. The mean max TTR knockdown after a single 25 milligram dose with approximately 83%, which was maintained for 90 days. Accordingly, this 25 milligram dose level was selected as the dose level for our Phase 3 pivotal study.

Importantly, in this Phase 1 study there were no serious adverse event and no discontinuations due to adverse events. All adverse events were mild or moderate in severity. Based on the data from the study, we predict approximately a 90% peak TTR knockdown level with vutrisiran after repeated quarterly dosing. Thus, we are anticipating based on the available data to-date that we will achieve TTR reduction with vutrisiran equivalent to that achieved with vutrisiran.

Now, John will further detail the HELIOS-A and HELIOS-B clinical study design.

John Vest

Executive Director, Clinical Research, Alnylam Pharmaceuticals, Inc.

Thanks, Rena. The HELIOS-A study will enroll approximately 160 patients with hATTR amyloidosis with polyneuropathy with a co-primary endpoint of mNIS+7 in Norfolk Quality of Life. The primary efficacy assessment for this open label study will occur at nine months and that assessment will be a comparison of the vutrisiran arm to the placebo arm of the APOLLO study which as you will recall is the pivotal study supporting the approval of ONPATTRO which readout in September of 2017.

Additionally, the HELIOS-A study itself will include a small reference comparator arm of patisiran dose patients. The study will include a 4:1 randomization which will result in approximately 120 patients receiving vutrisiran dosed once every three months at 25 milligrams and approximately 40 patients receiving patisiran dosed once every three weeks at 0.3 milligrams per kilogram. All patients will undergo a thorough efficacy assessment at month nine. A similar efficacy assessment will also take place at month 18 and patients may participate in a treatment extension portion of the study all receiving vutrisiran and thereafter. Again, the co-primary endpoints will be the change from baseline on both mNIS+7 in Norfolk Quality of Life.

Secondary endpoints will support a comprehensive assessment of disease burden is will include 10-meter walk test, modified BMI and an assessment of the patient's ability to conduct activities of daily living. Additionally, at the nine-month time point TTR reduction in vutrisiran-dosed patients compared to patisiran-dosed patients will be assessed.

Given the encouraging findings from the postdoc analysis conducted in APOLLO, we are prospectively specifying additional secondary endpoints on all cause death and all cause hospitalization, which will be assessed at the 18-month time point in the HELIOS-A study. Finally, exploratory endpoints will include cardiac measures such as NT-proBNP and Echo parameters.

There are a number of important design elements that went into HELIOS-A to optimize that study in a way that addresses patient needs [ph] be in (00:55:08) support swift and comprehensive clinical development for vutrisiran. First, from a study structure perspective, since vutrisiran harnesses the power of the RNAi mechanism, we can leverage much of what we know from patisiran in predicting TTR knockdown, potential clinical benefit and determining the optimal sample size for the study. Because we can leverage the data from the placebo arm of the APOLLO study for our primary comparative group, all patients on the HELIOS-A study will receive active therapy, a major benefit for patients with a rapidly progressive disease.

The cross-study comparison is also supported by the similarity in patient populations across the studies. The inclusion, exclusion criteria of HELIOS-A will be very similar to those of APOLLO. Patients will have a confirmed genetic mutation and a Neuropathy Impairment Score or NIS between 5 and 130, just like APOLLO.

Our inclusion, exclusion criteria will again resolve in a study population that will include multisystem disease manifestations and a range of disease severity. Also marrying APOLLO prior tetramer stabilizer use, following a washout period will be permitted for patients enrolling in the HELIOS-A study.

The study will have a global footprint as part of Alnylam's commitment to hATTR patients around the world. Enrollment is expected across North America, Western Europe, Asia, and other regions to ensure various mutation types are represented within the study population. The statistical analyses used in HELIOS-A are possible because from the patient-level data we have from APOLLO. Furthermore, many of the same well-established clinical assessment tools that were used in APOLLO for a thorough evaluation of disease burden in

patients with hATTR amyloidosis will again be applied in the HELIOS-A study to assess the change in neuropathy impairment, quality of life, ability to conduct activities of daily living and cardiac manifestations of the disease.

Now, for the first time I'd like to walk you through the HELIOS-B rationale and study design. Basically, we think of the APOLLO, APOLLO-B and HELIOS-A studies as building blocks that are all contributing relevant data to shaping the HELIOS-B design and the potential data package it will generate. APOLLO was the landmark study that confirmed the benefit of patisiran in the RNAi mechanism in patients with hATTR amyloidosis with polyneuropathy. The cardiac data from that study gives us reason to believe that patisiran and the RNAi mechanism have the potential to benefit a broader group of patients with ATTR amyloidosis.

So, now, we're actively assessing patisiran in patients with ATTR amyloidosis with cardiomyopathy. To get in the RNAi therapeutic the patients with ATTR amyloidosis with cardiomyopathy as swiftly as possible, the APOLLO-B study will utilize a functional endpoint, 6-minute walk test, because we anticipate seeing a benefit relative to placebo as early as 12 months.

In parallel, with vutrisiran, we're running the HELIOS-A study, which has the potential to be the first study with vutrisiran to confirm efficacy and safety of that product. We're leveraging this comprehensive body of background data, our deep understanding of RNAi therapeutics and years of experience in the ATTR amyloidosis field to establish a robust and compelling HELIOS-B study design. This study, the Phase 3 pivotal study for patisiran in patients with ATTR amyloidosis with cardiomyopathy has the potential to establish mortality and cardiovascular hospitalization outcomes data as well as the long-term treatment benefit of sustained TTR reduction in these patients.

Here, I will review the details of the HELIOS-B Phase 3 study design. The study will include approximately 600 patients with ATTR amyloidosis with cardiomyopathy. They may have either wild-type or hereditary disease and up to 30% of the total study population may be on commercial tafamidis at the time of randomization. Patients will have a medical history of symptomatic heart failure and NYHA class equal to or less than 3 and meet minimum criteria for 6-minute walk distance and NT-proBNP levels at baseline.

Patients will be randomized 1:1 to receive vutrisiran 25 milligrams subcutaneously delivered once every three months or placebo. The primary endpoint of the study is a composite outcome of all-cause mortality and cardiovascular hospitalizations. Patients will remain on the study for up to 36 months with variable follow-up such that the double-blind portion of the study will end and the primary endpoint will be assessed when the last patient completes month 30.

Secondary endpoints will include a compressive assessment of cardiac disease burden including6-minute walk test, quality of life, imaging assessments, and NT-proBNP. The study design also includes an optional interim analysis. We are actively working to start-up activities with this global study and we anticipate study initiation by the end of this year.

Now, Eric will speak more broadly about the TTR franchise as a whole and what the potential of the two RNAi therapeutic options will mean for patients.

Eric Green

VP & General Manager-TTR Program, Alnylam Pharmaceuticals, Inc.

Thank you, John and Rena. As we've discussed on the last hour, Alnylam's TTR amyloidosis franchise includes two distinct RNAi therapeutics, one approved therapy ONPATTRO for patients with ATTR amyloidosis with

polyneuropathy and one investigational therapy vutrisiran in the development for the full spectrum of ATTR amyloidosis. [indiscernible] (01:01:24) now have a good understanding of each of our programs and our plans with each.

So with these two products, our goal is to build a leading TTR franchise to serve the needs of patients for years to come. As we have seen, ONPATTRO is establishing a strong foundation and a transformational medicine to treat the polyneuropathy of hATTR amyloidosis in Europe and – sorry – in the U.S. and in Europe to treat hATTR amyloidosis in patients with stage 1 or stage 2 polyneuropathy. We believe that by complementing ONPATTRO with vutrisiran, we will establish a franchise of treatment options we will deliver significant benefit for patients and for our businesses.

There are a number of benefits to establishing a franchise approach in the ATTR amyloidosis area. Continued investment and innovation is supported by ONPATTRO revenue, a deep understanding of the burden of this devastating disease, longstanding working relationships with key thought leaders and centers of excellence and the ability to leverage an existing global footprints with the launch of additional therapies for all meaningful contributors to maximize the potential of patisiran and vutrisiran individually, but also as a portfolio as a whole.

Additionally, the benefit of patients and physician choice is key. The ability of multiple RNAi therapeutics in this space will eventually enable patients and physicians to select an option that best addresses the uniquely individual set of needs for these patients. Importantly, ONPATTRO will remain an attractive option for many patients and their physicians. For patients who are receiving benefit from ONPATTRO, we believe and will likely desire to remain on treatment.

The vutrisiran has the potential to have the most competitive product profile considering a range of factors including efficacy, safety, dose and schedule of both current and emerging therapies. The HELIOS development program is designed to generate data to affirm this potential.

Importantly, discovery and development of great medicines is meaningless if patients who could benefit don't have access to them. We will continue to build on a proactive approach with payers that we have already established with ONPATTRO. We will diligently work to ensure broad access for patients by continuing to drive innovation in all that we do.

Another view of our TTR franchise strategy and how it builds over time is shown here. Again, the APOLLO study established a strong foundation for the franchise with ONPATTRO in patients with hATTR amyloidosis with polyneuropathy including those with a mixed phenotype. And with the approval of ONPATTRO, we established RNAi as a whole new class of medicines. And ONPATTRO became the first and only treatment to demonstrate the reversal of neuropathy manifestations in the majority of hATTR amyloidosis patient study.

Over the next few years, we expect two pivotal clinical study readouts specifically HELIOS-A and APOLLO-B. With the HELIOS-A study, we anticipate the initial launch of vutrisiran into the hATTR amyloidosis patient population. Vutrisiran is expected to have similar efficacy profile to that of ONPATTRO and we anticipate that will also have an acceptable safety profile as well. Uniquely, vutrisiran has the potential to offer patients the certainty of sustained TTR knockdown for 90 days after each subcutaneously administered dose and to provide a highly convenient treatment regimen for patients and the healthcare system.

Also in the timeframe, the APOLLO-B study is expected to build on the exploratory [ph] and other cardiac (01:05:01) data from the pre-specified cardiac subpopulation in APOLLO and potentially enable an expansion of the indicated patient population to include patients with ATTR amyloidosis with cardiomyopathy.

In the longer term, 2023 and beyond, we believe vutrisiran achieves sustainable market leadership with mortality and hospitalization outcomes data from the HELIOS-B study. If we achieve high impact cardiac outcomes data from the study, we believe we have the potential to solidify a compelling data package and a competitive product profile.

In summary, with ONPATTRO achieving approval and access and in more and more countries, with improving diagnosis and patient finding and with continued evidence generation efforts highlighting the differentiated features of ONPATTRO, we are encouraged to see continuous and steady growth and we're confident in our future commercial potential even in an increasingly competitive environment.

Moreover, as we look over a longer time horizon, we believe there are a significant growth opportunities for our overall ATTR amyloidosis franchise, including to potential label expansion for ONPATTRO in both hereditary and wild-type ATTR amyloidosis patients with cardiomyopathy and also the advancement of vutrisiran, our once quarterly subcutaneous investigational RNAi therapeutic into potentially all segments of the ATTR amyloidosis market. We're very committed to being the leaders in ATTR amyloidosis space and we believe our efforts position us well for the future.

This is an exciting time for Alnylam and a hopeful time for patients with ATTR amyloidosis. We sincerely thank our patients who have been and will be a part of this journey with us. I can honestly say, we keep patients top of mind in all we do and we are deeply committed to our ATTR community.

With that, we will now move over to some questions.

QUESTION AND ANSWER SECTION

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

A

So, as a reminder, please submit your questions by clicking the ask a question button located above the side window of the webcast player.

I think we start with some questions. Maybe, Mike, if you don't mind, we have a few come in for you.

Despite your family history, Mike, you were hesitant to be genetically tested for symptoms before the symptoms manifested you said, at the time, due to a lesser treatment options. I think we hear many people still struggle with that decision to test and to share the information with family who may also be at risk. Do you have any advice on what you could have folks do that remained hesitant to be tested?

A

Yeah. Thanks, Eric. Like I said, I did hesitate to get tested because there were no treatments at the time and I didn't want to – like in my story, I shared I didn't want [indiscernible] (01:07:51) stomach and pain to the disease. However, with treatments now available and for those who have a family history, I suggest they speak with their physician about getting tested. Also speaking to a genetic counselor can help aid in the process of making that decision as well. That was very helpful for me.

One of the most important things I did learn about the disease is early diagnosis, and that's key. And I really feel fortunate that I took action once I experienced those symptoms that I had.

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

Thank you, Mike. In your view, not even on ONPATTRO for a while, patisiran initially, what has been the most significant change in your symptoms?

I think the progression of my symptoms was quite dramatic at first. It began to really interfere with my life. It was difficult focus at work because I knew the – most of the patients diagnosed with the disease back then. I know what my dad had. I had more pains in my hands, the numbness wouldn't go away. I remember times at work when I had to get up and walk around a few times. Really, a few times an hour just to get the numbness to go away. So, I really had – really difficult progression in a very short period of time.

Now, I think with me being on ONPATTRO, I don't have to walk away from my desk anymore. I don't have the numbness and tingling. I don't have to wear socks at home when relaxing because my feet don't feel like ice. I'm employed, so I can fully focus on my work and also my family, which is really important to me.

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

That's good. Thank you, Mike. Some of those symptoms you mentioned that initially you noticed, how those changed over time? Have you noticed any difference?

Yeah. So, like I was saying, the numbness and tingling only happen to me at night when I sleep right now and they only happened in my hands. Prior to me being on ONPATTRO, I would sit down at work and it would be my hands would go numb, my feet would go numb and my legs up until my knees would go numb within a matter of minutes. Right now, I can enjoy my life. I can enjoy spending time with my kids. Like I mentioned in my story, I love to spend time with them playing lots of sports and travel with my family, and that's all things I can now do, and because of ONPATTRO and I feel the benefits and the symptoms have definitely decreased.

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

That's great. Thank you, Mike. I think we have couple of questions on some of the other programs, so we may come back to you if we have more time. [ph] As the (01:11:00) questions coming in, maybe a somewhat simple one, John or Rena, what is the volume of injection for vutrisiran given the 25 milligram dose?

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

The volume in – for vutrisiran is about [ph] 0.5 million for (01:11:21) injection once every 90 days...

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

A

Yeah.

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

A

...for subcutaneous injection.

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

A

Very low dose and very low volumes [indiscernible] (01:11:29) will be obviously explained how that is tolerated throughout the studies.

Similar question [indiscernible] (01:11:36) mind, why is HELIOS-A study open-label? What were the considerations for that design?

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

A

Yeah. Thanks. That's a great question, and it was one of the things that we're really pleased to be able to have an open-label study where everybody is receiving active therapy, again, with this rapidly progressive disease, something that we're very pleased to offer. We felt that given the vast experience that we had from the APOLLO study, the access to patient-level data from that study we're able to leverage the placebo arm from that historic study as the primary comparator group for HELIOS-A, thus we decided on the open-label approach.

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

A

That's great. And kind of following question, how is it going with HELIOS-A? How is the enrollment?

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

A

Yeah. What we are actively getting new sites up and running. Every day we're hearing a great deal of enthusiasm from our investigators and we're very, very pleased.

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

A

Great. Maybe pivoting to the B studies, both APOLLO-B and HELIOS-B. Maybe you could talk a little bit about the considerations and why we have two different studies in a similar patient population?

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

A

Yeah, thanks, another great question. As we – you're trying to highlight [indiscernible] (01:13:09) in the presentation APOLLO-B with patisiran, we are anticipating that as a data package with the 6-minute walk test that will get us as quickly as possible to enable that offering for patients with ATTR amyloidosis with cardiomyopathy and then that would then follow on with the larger and longer study with patisiran to establish a mortality benefit that in these patients. So we, overall across the program, view these as complementary programs that will – we

hope eventually enable both patisiran and vutrisiran to be an offering that's available to all patients with this disease.

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

A

Great. And with the HELIOS-B design and obviously [ph] as more (01:14:03) details we have previously, has this been discussed with regulatory agencies?

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

A

Yes, absolutely. We have vetted this design with global regulatory authorities, and they're aligned on our approach.

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

A

Great. And maybe, Rena, to you, how are we thinking about trying to find patients that are all involved APOLLO-B and HELIOS-B especially given approval to [indiscernible] (01:14:29) here in the U.S. and potentially elsewhere over time?

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

A

So, as we're thinking about this patient population, there's obviously, the inclusion, exclusion criteria for each study. But it's important that the physicians work with the patients to identify what treatment option would be most suitable for them. Certainly, we're excited about the clinical study options and the potential for these molecules in the clinical setting.

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

A

Great. Maybe Mike we'll come back to you for one last question, this is the most appropriate way to end today. Maybe, if I may, what's been your experience like at your infusion center while you're in Boston since you lived in Philly? And then now that you moved closer to home for your infusion, how is that gone?

A

Yeah, sure. Traveling to Boston was a priority for me. Any other alternative was not an option. Like I said in my story, I was able to work remotely on those days and utilize the Family and Medical Leave Act to ensure that my time for infusions were accounted for. My family and I like to travel and we're also big sports fans, as I mentioned, and this worked out well as I took each of my kids with me on separate trips to Boston for some time away with dad. We were also able to catch some of the sights of Boston while we were there; we enjoyed the Red Sox and the Celtics game and always had time for another lobster roll.

The transition from Boston to Philly was fairly smooth. I did have some wonderful nurses and physicians in Boston that had grown fond of because they're always there for me when I had questions and was able to connect with them and the team every three weeks when I had went in. So leaving that was a bit tough, but the infusion center in Philly is definitely more local to me and allows me to save on travel costs as well.

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

A

That's great. Glad to hear that. I think with that, we are probably [ph] at a time (01:16:33) so I will again thank you very much Mike for your willingness to join us today and talk about your experiences. Thank you to John, to Rena. And with that, I'll turn it back to Josh.

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

Thanks, Eric, and thanks to all of our speakers. This concludes our RNAi roundtable for today. The replay and slides will be posted on the Capella section of the Alnylam website later today, with the transcript to follow shortly thereafter.

Please join us for upcoming RNAi roundtable for givosiran on October 7 and for lumasiran on October 10. And finally, we encourage you to save the date to join us for Alnylam's 2019 R&D Day in New York City on November 22.

Thanks, everyone. Have a good day. You may now disconnect.