ALNY - Alnylam Pharmaceuticals Inc RNAi Roundtable: Patisiran and Revusiran for the treatment of Transthyretin (TTR)-Mediated Amyloidosis

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OVERVIEW:
Co. provided an update on patisiran and revusiran for the treatment of transthyretin (TTR)-mediated amyloidosis.
Good morning, everyone, and thank you for joining us for our RNAi Roundtable to discuss the progress we are making with patisiran and revusiran in development for the treatment of transthyretin-mediated amyloidosis.

I'm Josh Brodsky, Senior Manager of Investor Relations and Corporate Communications at Alnylam. With me today are Barry Greene, President and Chief Operating Officer; Dr. Philip Hawkins of the National Amyloidosis Centre; Isabelle Lousada, President and CEO of the Amyloidosis Research Consortium and Chairman of the Amyloidosis Foundation; Eric Green, Vice President and General Manager of the TTR Program at Alnylam; and Dr. Jared Gollob, Vice President of Clinical Research at Alnylam. I will be turning it over to Barry in just a moment, who will provide you with a brief introduction, but first a few comments.

Today’s RNAi Roundtable focused on our patisiran and revusiran programs is part of a series of Roundtables that we are hosting this July, August, and September. Today’s event will end at around 10:30 AM Eastern Time. We will be hosting two Q&A sessions, and you may submit a question at any time during the webcast by clicking the Ask a Question button located above the slide window on the webcast player. Barry will moderate a Q&A session with Dr. Hawkins and Isabelle, and then again with Eric Green and Jared Gollob 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. With that, I will turn it over to Barry.

Thanks, Josh, and good morning, everybody. I’m thrilled to be here today to review our ATTR program with Eric and Jared, and I’d very much like to thank Philip and Isabelle for joining us on the call and spending their valuable time with us.

As you’re aware, Alnylam is developing a broad platform of RNAi therapeutics and our approach, we believe, has developed into a reproducible and modular platform. Our strategy is to target genetically valid targets in the liver; achieve rapid proof-of-concept in Phase 1, as we’ve seen with multiple programs; and then have very clear, defined paths to market.

As you’re aware, we’re developing programs across our three Strategic Therapeutic Areas: our Genetic Medicines STAr, our Hepatic Infectious STAr, and our Cardio-Metabolic STAr. Today, as you’re aware, we are focused on our TTR program: patisiran, which we’re developing for FAP,
revusiran, which we’re developing for FAC, both in Phase 3 trials; and, very importantly, ALN-TTRsc02, which we’re developing as a follow-up to those molecules, where we believe we can achieve once-a-month or once-a-quarter subcutaneous dosing.

So thank you again, and with that I will turn the call over to Philip.

Philip Hawkins  -  National Amyloidosis Centre  -  Head

Thank you very much. I’m going to give a talk for about 20 minutes on what amyloid is, and some of the clinical aspects of ATTR amyloidosis, and what the standard of care for treatment is at the moment.

Firstly, the amyloid substance: amyloid, the protein substance, is a collection of abnormal extracellular protein deposits which are composed of amyloid fibrils, which build up in tissues throughout the body, damage the structure of those tissues, and lead to organ dysfunction. Amyloid can be identified by the Congo red stain under the microscope in biopsy sections.

The amyloid diseases are categorized according to the amyloid protein in question. But essentially, all types of amyloid have a similar pathology, a similar abnormality of protein misfolding leading to the buildup of essentially similar amyloid fibrils.

Next slide, please. This is a slide showing appearance of amyloid and an extracellular space in the top panel, under the electron microscope, this meshwork of fibrils. The three panels under that show amyloid staining with Congo red on the left in glomeruli in a patient with renal amyloidosis, and other special stains that we use for confirming and typing the particular protein.

Next slide, please. Amyloidosis is the -- are the diseases that are caused by the accumulation of amyloid deposits. Systemic forms of amyloidosis are usually fatal and we think cause about 1 in 1,000 deaths in the Western world, with AL amyloidosis -- monoclonal light-chain amyloidosis -- by far the most frequently diagnosed type.

Most patients are diagnosed late in the course of their disease, when there are substantial amounts of amyloid in the affected organs, and treatment in all types remains very challenging. However, there have been great advances in our understanding of the molecular basis of these diseases. But nevertheless, there is still major unmet medical need.

Next slide, please. So the amyloid causes disease probably, in the main, simply by their physical presence. The deposits build up in the interstitium and lead to structural damage and functional impairment.

Certainly there is no situation in amyloidosis where you get disease and organ dysfunction without the presence of amyloid. And in general one can show that organ dysfunction worsens as the amount of amyloid builds up over time.

However, it is possible in some types of amyloidosis to see regression of the deposits, in situations where it has been possible to switch off the supply of the respective amyloid-forming protein. Regression of amyloid occurs slowly over months and years; but when it occurs, one sees clinical benefit, improvement in organ function, and much better survival of patients.

Early diagnosis is obviously important. There are great efforts by us and other people in the world to promote amyloid awareness. And there are considerably improved diagnostics coming onto the horizon, which will be of particular benefit in ATTR type.

Next slide, please. In hereditary transthyretin -- ATTR -- amyloidosis, the amyloid fibrils derive from genetically variant transthyretin protein. This disease presents either as familial polyneuropathy, FAP, or familial amyloid cardiomyopathy, FAC.

It’s thought that there are several tens of thousands of individuals around the world with hereditary amyloidosis. FAP occurs in some particular pockets in Portugal, Sweden, Japan.
There are collections of patients with the TTR Met30 mutation, who are generally less than 40 years of age and present with peripheral and autonomic neuropathy. Cardiac involvement in those patients is rare. The disease progresses to death over a period of about 10 years.

In the UK, the transthyretin alanine 60 is the most common variant. This disease presents either as peripheral neuropathy, autonomic neuropathy, or as cardiac amyloidosis, or any mixture of the above, usually beyond 60 years of age. Cardiac deaths usually occur within five years.

The most common form of familial amyloid cardiomyopathy, FAC, is associated with the TTR isoleucine 122 genetic variant, which occurs predominantly in black individuals, but not exclusively, and in about 4% of black African-Americans. The penetrance of this is unknown, but we presently think that this disease is much underdiagnosed. Cardiac amyloidosis develops after about age 60 and death occurs within five years, most commonly within two to three years in patients with this mutation.

Next slide, please. The clinical course of FAP can be very simply broken up into three stages: where the patient is ambulant, ambulant with assistance, and Stage III where they are no longer ambulant. In addition to the symptoms of peripheral neuropathy and loss of sensation and strength in the limbs, there may be autonomic symptoms of varying degrees, often severe at the end of the disease, causing weight loss, constipation, diarrhea, difficulty eating, low blood pressure. Essentially this becomes a wasting disease.

Next slide, please. These images show patients with different stages of the disease and approximate time course between each stage. Many patients are not actually diagnosed until the latter stages of Stage I; and therefore their expected survival may be in the order of just about five years or so.

Next slide, please. The clinical course of FAC is that of progressive heart failure, with diastolic dysfunction and, in the latter stages, systolic dysfunction. Symptoms are those of left- and right-sided heart failure including fatigue, shortness of breath, reduced exercise tolerance, fluid retention, enlargement of the liver, loss of appetite, nausea, and so on.

Patients often have conduction abnormalities including atrial fibrillation and heart block, requiring insertion of pacemakers and sometimes other devices. As the disease goes on there are frequent hospitalizations for cardiovascular decompensation, heart failure symptoms, and unpredictable death.

This is — the next slide shows a postmortem slice through a heart showing gross thickening of the left ventricle, which you can see is about 2, 2.5 centimeters thick here. This represents a mass of amyloid in the interstitial space between the heart muscle fibers. A normal left ventricle should be no more than 11 to 12 millimeters thick.

Next slide, please. The disease FAC is likely to be identified when a patient develops heart failure symptoms and undergoes echocardiography, which is very widely available and, as you can see on this slide, shows a diffusely thickened heart wall, consistent with the slide I've shown you previously. Cardiac MRI is much more sensitive and specific than echocardiography and is a developing investigation that is much more widely available than before. In general, cardiac MRI even in inexperienced hands in this disease will identify the diagnosis.

Next slide. Further, we and others have been investigating the use of bone scan — scintigraphy — either with technetium-labeled DPD in Europe or technetium-labeled pyrophosphate in the States, which both do the same thing and, as you can see here, localize into the hearts of patients with ATTR amyloid. All patients with clinical symptoms due to cardiac ATTR amyloid will have a Grade 2 or so-called Grade 3 DPD or PYP scan. This type of scintigraphy is incredibly sensitive for the diagnosis of the disease and potentially should become available in all hospitals with nuclear medicine facilities, which essentially is any hospital in the Western world. So DPD scintigraphy is a big advance in the diagnosis of this disease; and in conjunction with genetic testing, and echocardiography, and exclusion of AL amyloid via light-chains in the blood and urine, will enable noninvasive diagnosis of these disorders.

Next slide, please. This shows an outline of current therapies for amyloidosis. The one of proven benefit, which has been demonstrated in AA and AL systemic amyloidosis, is on the left, i.e., a reduction in the supply of amyloid precursor protein, which inhibits the buildup of further amyloid deposits and enables existing amyloid deposits to gradually regress over the fullness of time. There are other treatments in development including...
immunotherapy directed towards the amyloid deposits themselves to promote their clearance and small molecule drugs like tafamidis and diflunisal that combine to and stabilize precursor proteins in the blood.

Next slide. So the treatment of amyloidosis as of now is -- of proven benefit are efforts to reduce the supply of the respective amyloid fiber precursor protein, i.e., in AA amyloidosis to control inflammation and reduce the production of SAA protein by the liver. In AL amyloidosis, chemotherapy directed towards the bone marrow plasma cell dyscrasias to reduce the production of monoclonal light-chains.

And in ATTR amyloid, the only treatment that is regarded as standard of care is liver transplantation to remove the source of the genetically variant amyloid-forming TTR protein. Thousands of liver transplants have been done in hereditary TTR amyloidosis to date.

Next slide, please. These show SAP scans in a patient with AA amyloidosis. In 1999, this patient having amyloid in the liver and spleen -- showing up as intense black on the image -- whose inflammatory disease was well suppressed, and two years later there's been substantial regression of the deposits visible in the 2001 SAP scans. So this shows the natural clearance of amyloid over a prolonged period.

We've shown in thousands of patients in AA and AL amyloidosis that more than 50% of the existing amyloid deposits can be cleared away by natural mechanisms when the amyloid precursor protein supply is cut off. In some organs this occurs more slowly; and in some patients it occurs more slowly.

Without any treatment, the clearance of amyloid is always slower than the ongoing rate of new amyloid deposition, and therefore progression of the disease. But the corollary of this is that any reduction in the supply of the amyloid precursor protein will necessarily slow down the buildup of amyloid and therefore disease progression. In some instances, and AL and AA amyloid we've shown that a 50% reduction in the precursor protein formation is sufficient to completely halt progression.

Next slide, please. So the medical -- the management of FAP is firstly relief of symptoms for neuralgic pain, gastrointestinal symptoms associated with autonomic disease, and symptomatic management of heart failure. This is effective to a point. But the only disease-modifying therapies to date have been liver transplantation to remove the source of the genetically variant TTR protein, and this has been effective to some degree in patients with early-stage Met30 disease -- patients who don't usually ever have cardiac involvement -- but it has not been very successful in patients with more advanced disease, and not very successful in all of the other mutations which are pretty much all associated with cardiac amyloidosis.

We have seen a progressive accumulation of amyloid in the heart and other sites following liver transplantation. So it seems that normal wild-type transthyretin is able to continue to be processed, misfolded, and deposited on the template of genetically variant amyloid that occurred before liver transplantation. Thus, it is falling out of fashion, particular for non-Met30 mutations.

TTR stabilizers have been studied, tafamidis and diflunisal. Both of these shows some promise, but I certainly have no personal experience with tafamidis, which was not approved by our National Health Service for reimbursement and therefore we've not been able to use it. We have been using diflunisal in our own clinic, but with no particular evidence, no real suggestion, that it is effective in cardiac TTR amyloid types.

Next slide, please. So the management of FAC is really relief of symptoms for congestive heart failure: diuretics, fluid balance management. Liver transplantation, for reasons I've described, has no role. And cardiac transplantation has been performed in a handful of patients, but mostly patients are too old to undergo this procedure and availability of hearts is too limited.

Next slide, please. This is a brief case history of a patient with typical TTR Met30, with early disease. She was a 36-year-old woman from Cyprus; two-year history of painful peripheral neuropathy and loss of bladder control. No cardiac amyloid.

The diagnosis was made relatively early because the disease was known in her family. She waited, however, two years for her liver transplant before an organ became available and during which time her neuropathy worsened.

However, she did stabilize following the transplant, put on weight. There was some recovery of bladder control and no worsening of her peripheral neuropathy; so she would appear to have benefited from liver transplantation.
Next slide. This is a patient with FAC associated with the isoleucine122 variant. He was unusually young: most patients are beyond age 70, but he was 59, an Afro-Caribbean man who presented with heart failure back in 2003. His echocardiogram showed thickened left ventricular and right ventricular walls with good ejection fraction, raising suspicion of amyloid which was confirmed by genetic testing that showed he was in fact homozygous for this variant.

The disease at that time was confirmed by cardiac biopsy and transthyretin staining on the tissue. He was accepted for a cardiac transplant, which was performed over 10 years ago, and he remains well. There has not been any recurrence of his amyloid on DPD or MRI imaging.

Next slide, please. So this disease remains a very serious one with substantial unmet need. Liver transplantation is still a reasonable approach, but pretty much just for patients with TTR Met30 and very early-stage disease; and this approach is no longer recommended in any patient with cardiac involvement.

The TTR-stabilizing small molecule drugs show some promise, though their efficacy has been rather limited in the studies performed so far. And there is no evidence as yet that they are efficacious in FAC.

So there is a robust rationale for reducing the supply of TTR in the plasma to treat FAP and FAC, a strategy that has proved to be highly effective in other, more common types of acquired amyloidosis.

At this point I would like to hand over to Isabelle Lousada, who is going to tell you about the Amyloidosis Research Consortium. Thank you.

Isabelle Lousada - Amyloidosis Research Consortium - President & CEO and Chairman Amyloidosis Foundation

Thank you, Dr. Hawkins. I’d like to thank Alnylam for holding this webinar and inviting me to take part.

There has been success since the first orphan drug legislation 30 years ago, and the future is bright for the development of drugs to treat rare diseases. We’re seeing advances in the development of new therapies and modalities such as RNAi therapies.

Next slide, please. There are 7,000 rare diseases and many of these are facing similar delays and challenges in clinical development, exacerbated by the years and many doctors patients face to get diagnosed. There’s a limited number of patients, leading to slow accrual of trials.

Considering rare diseases affect more than 25 million Americans, it’s critical to address these challenges across the board. One of the keys is active engagement and alignment on the important issues between key stakeholders in the development of rare disease therapeutics including industry, regulatory authorities, research funding bodies, and patient associations.

Next slide, please. Patient engagement and patient-reported outcomes are hot topics, and I’m going to talk a little bit about the expanding role of patients and advocates, both in the drug development continuum and also in patient engagement. Medical products and interventions that begin with a solid understanding of patient needs and expectations really promise better outcomes for the individuals, families, and communities.

Next slide, please. Just to touch briefly on the history of patient engagement, in 1938 the March of Dimes, an initiative which was founded by Franklin Roosevelt whereby individuals contributed to and expanded research into polio, and this led to the development of the iron lung. For most of history, patients were passive recipients of medical care and with little or no input.

In 1947 the Nuremberg Code was introduced and introduced informed consent, and in 1973 the Patients’ Bill of Rights was introduced. Patients often didn’t expect to hear their diagnosis and much less have a voice in determining their care plan.

Then in the 1980s the HIV/AIDS activists charted a path forward for the way patients can engage in all aspects of research and delivery of care, under stunningly difficult circumstances.
We're at a turning point in the evolution of patient engagement. The US federal government initiated a series of efforts to elicit and include patient perspectives along the full range of clinical development such as PCORI, which is the Patient-Centered Outcome Research Institute established through the Affordable Care Act; the Patient-Focused Drug Development Initiative at the FDA mandates it under PDUFA V; and this year, the 21st Century Cures Initiative, which has solicited unprecedented public input about how Congress could help accelerate the discovery, development, and delivery of promising new therapies and cures for patients.

Next slide, please. One can effectively incorporate the patient’s perspective at multiple points along the drug development continuum, which can be defined: as encompassing R&D portfolio selection and prioritization; identification of research questions, outcomes, and comparators; clinical trial design and recruitment strategy; regulatory review; and commercialization and post-market surveillance. By being patient-centric and adding transparency and interaction all along the R&D and market lifecycle, patients help to achieve best outcomes.

Patients have a valuable contribution to make to the science, and the patient-reported outcomes should be used as part of the supporting data in clinical trials. I won’t go into too much detail on this slide, which shows at every stage how advocates can represent patients in the drug development process.

But in the prestudy they can help define the unmet medical needs, therapeutic burden, meaningful surrogate or direct clinical trial endpoints, and risk-benefit tolerance and preference. They can also fund research and product development.

Engaging patients in clinical trial design can help improve the study’s efficiency by addressing barriers to participation, recruitment, protocol compliance, and retention. Patient groups are second to doctors in being seen as trustworthy sources of information and so can really support trial awareness and recruitment.

During Phase 2/3 studies they can provide feedback on how the patient community views results. During the FDA review and approval, patients serve on the FDA Advisory Committees and provide testimony at FDA hearings. And postapproval, they can share product information with the patient community.

Next slide, please. There are some good models that address the challenges rare diseases face in clinical trials, and strength is gained from collaborating with other disease groups. However, we always need to make sure that we’re not just a number in 7,000 and that we address the particular and unique challenges of our stakeholders. We need to be clear about the challenges and burden of disease that people affected by amyloidosis face.

Amyloidosis is a complex group of diseases with a heterogeneous population. I’ve heard a number of people talk about a mystery illness that has affected generations of a family and the relief at finally knowing what it is. For others without a known history, it can take many visits to different specialists and multiple years to know what ails them, and they talk about the extreme isolation of being diagnosed with a rare disease.

But what does it really mean to someone who is affected by this? There is a young man who describes so vividly as a child watching generations of his family suffer. He talks about being exposed to the loss of his grandmother at a very young age, and he was too young to understand the effects of the disease; then when he was old enough to understand the suffering, watching his aunt who, unable to live alone, had moved in with them and quite literally wasted away.

In his early teens, being mortified as the disease struck his mother: not that she walked on crutches but that his friends should see her Depends as he unpacked her grocery bags. And then in his early 20s starting to have episodes himself of dizziness, fatigue, he had a feeling of numbness in his fingers and arms, and was finding it hard to hold a pen or play the guitar. But harder still for him was becoming incontinent in public and suffering from erectile dysfunction, so all his dreams of future and family of his own were erased.

His younger sister has started to be symptomatic now. And what he wished for more than anything -- he is realistic and understands the time it takes to get novel therapies approved, but his hope is that his little niece will not suffer the same fate. And if she has this awful disease, he hopes that there will be an approved and effective therapy.
With a small pool of patients and a growing number of clinical trials, there is concern that enrollment may be slow and delaying trial. And the regulatory process is arduous and with single agents landing in multiple regulatory divisions and a lack of in-house expertise, that causes more challenges.

There is a potential for multiple therapies, and that will add complexity to the landscape. Companies might feel dis-incentivized to take part in clinical trials. But we fight so hard to get a treatment, because of the many faces we see for a disease that quite literally destroys quality of life years before a patient dies.

Next slide, please. In a survey that we carried out of 553 amyloidosis patients -- interesting statistics, which show that 73% believe that participating in a clinical trial would enhance their overall care. 49% of patients say they have no or little access to information on clinical trials which pertain to them.

45% say if they were well informed about a clinical trial they would consider taking part. 73% of patients say they're unsure how to enroll in a clinical trial.

This is a moment in time where the course of amyloidosis is changing. It's easy to point out the problems, but to move forward they need to be systematically addressed, and we need to collaborate to come up with solutions.

Next slide. I represent The Amyloidosis Group which consists of the Amyloidosis Foundation, which is focused on empowering patients and their families through a comprehensive range of services, from providing information to support, to holding patient educational meetings. The AF also puts on Grand Rounds to educate physicians, and holds awareness meetings at major medical conferences, and gives both research and travel grants to physicians and researchers.

The clinical trial finder is a tool that, as a result of our survey, we're starting to build, which will help educate patients and direct them to trial. It will also act as a registry able to direct a pool of waiting patients to new trials as they open.

Although the major centers of excellence in amyloidosis see many patients and the majority of patients, from our survey we learned that about 38% of patients don't get to these centers and many of these are missing the opportunity to take part in a clinical trial. So this will be a vital tool to speed up trial accrual and also help identify unmet need.

It's not enough to just be the voice of the patient. To effectively expedite change, it takes consistence, collaboration, and creating a well-defined roadmap.

The Amyloidosis Research Consortium was established this year to address critical needs in clinical trials and related research for the underserved group of systemic amyloidosis diseases, to systematically address and remove the critical barriers and challenges that are slowing down or preventing the research, development, and access to new effective treatments and optimal care, by building mutually beneficial collaborative relationships between government, academia, patients, industry, and regulators. The ARC is built around a clinical trial network of amyloidosis centers of excellence that are driven by the shared goal of conducting trials more efficiently and collaborating on innovative studies which will in turn, we hope, speed the delivery of new and better therapies for patients. Thank you.

**QUESTIONS AND ANSWERS**

**Josh Brodsky** - *Alnylam Pharmaceuticals, Inc. - Senior Manager IR & Corporate Communications*

Thank you very much. We are now going to open it up for Q&A with Dr. Hawkins and with Isabelle. As a reminder to those listening, please submit your questions by clicking on the Ask a Question button located above the slide window on the webcast player.
Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Thanks, Josh. And again, thanks Philip and Isabelle for that fantastic overview. We're going to field questions.

The first question is a basic question for Philip, which is: Why do you believe that RNAi is a reasonable approach to pursue ATTR?

Philip Hawkins - National Amyloidosis Centre - Head

Well, there's a very simple answer to that, in that RNAi, which can substantially reduce the production of transthyretin, must necessarily substantially reduce the formation of new transthyretin amyloid and therefore greatly prevent the ongoing buildup of transthyretin amyloid in the hearts and nerves of these patients. The reduction in amyloid precursor proteins in AL and AA amyloid has been incredibly effective treatment, and there's no reason to suppose that it won't be in TTR type.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

A follow-up to that that came in online: Where did the 50% reduction come from? And do you believe that the more we can reduce TTR levels the better effect we'll see? Is there a correlation there?

Philip Hawkins - National Amyloidosis Centre - Head

Yes, there is. The importance of the 50% figure that I quoted is that a reduction by 50% in the concentration of the amyloid precursor protein in some patients is enough to actually see net regression of their amyloid deposits in AA and AL amyloid. In other words, the natural clearance of amyloid becomes greater than the accumulation of new amyloid.

Now, of course, greater reduction is better. And in AA and AL amyloid these days we are hoping to see 80%, 90% suppression of the precursor proteins when we see a new patient, because we know that 80%, 90% suppression will have the best possibility of clinical benefit and will have a great clinical benefit in most cases.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Great, thank you. There's a question about diagnostic methods in general, and I think it's focused more on FAC. You mentioned that we're not sure of the penetrance of FAC. While the numbers might be large, the penetrance is unclear.

Could you describe what's going on in the world of diagnosis? And can the diagnosis methods differentiate between different kinds of amyloidosis?

Philip Hawkins - National Amyloidosis Centre - Head

Yes. At the moment FAC, say, typically perhaps in a patient with the V122I variant, will present with a variety of heart failure symptoms or conduction abnormalities, and a patient will almost always go on to have an echocardiogram. The echocardiogram in this disease will show diffuse thickening of the left ventricular and right ventricular walls; and one would hope that those images will suggest the diagnosis of amyloid to the cardiologist looking after the patient.

These days, many such patients are now routinely being put forward to cardiac MRI, on the suspicion of an infiltrative cardiomyopathy, or just because cardiac MRI is available. And the images on cardiac MRI following gadolinium contrast, and even without, are very, very characteristic of the disease in every case. The diagnosis is unlikely to be missed at that stage.

The cardiac MRI will more or less confirm the diagnosis of amyloidosis. It will not tell us what type of amyloid is present.
By contrast, DPD or pyrophosphate scintigraphy is very, very much more specific for cardiac amyloid of TTR type. Every single patient will have an abnormal DPD or PYP scan.

Some patients with AL amyloidosis, a small minority, can also have positive DPD and PYP scans. However, the diagnosis can be corroborative of FAC by simple genetic testing, sequencing of the TTR gene; and the possibility of AL amyloidosis is excluded virtually completely by undertaking screening of the blood and urine for monoclonal immunoglobulin.

So the presence of a TTR mutation and the absence of a monoclonal immunoglobulin in the presence of heart failure with a positive DPD or PYP scan secures the diagnosis of FAC. I’m sure that the way forward, what we will see, is much more widespread uptake of these technetium scanning techniques to look for this disease in older patients with heart failure and preserved ejection fraction.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Great. We’ve got a question for Isabelle. Isabelle, what are the top priorities for the Amyloidosis Research Consortium and Amyloidosis Foundation? What are the top one or two priorities, if you could highlight those?

Isabelle Lousada - Amyloidosis Research Consortium - President & CEO and Chairman Amyloidosis Foundation

Yes, I think one of the biggest priorities is raising awareness of the disease to get an earlier diagnosis. I think a lot of patients are too sick by the time they get diagnosed to benefit from treatment.

I think the other priority is setting up with the Consortium a big meeting with the FDA and all the experts to really look at making clinical --facilitating clinical trial design and accelerating the development for the review of potential therapies.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

That’s great. Thank you. Just a follow-up to that question on, I guess, attitudes of patients. With potential therapies on the horizons, be they stabilizers or an RNAi therapeutic, do you see that the patients and their families are more willing to be diagnosed or to bring their family members in for potential diagnosis than in the past?

Isabelle Lousada - Amyloidosis Research Consortium - President & CEO and Chairman Amyloidosis Foundation

Yes. I think it varies very much between families, but I think absolutely. I think it’s also reflected in the number of patients that really actively are looking to participate in clinical trials.

So I think there is really great hope about what’s on the horizon for patients.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

I guess a subset of that question specifically coming in from people listening to the call, is that people of African descent, particularly the African-Americans, have not been not willing to participate in clinical trials. How do you feel that’s going in the United States and Europe right now? And maybe Philip can comment on that as well.
Philip Hawkins - National Amyloidosis Centre - Head

Well, this has often been said. But we are participating in the Alnylam ENDEAVOUR study, and we are finding participants, black individuals with isoleucine 122-related cardiac amyloid, were very willing to participate in this study – rather more easily than we thought.

I guess the knowledge of an effective treatment as it emerges will be the most powerful means by which at-risk groups will become engaged with this.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Great. Isabelle, any perspective on that?

Isabelle Lousada - Amyloidosis Research Consortium - President & CEO and Chairman Amyloidosis Foundation

Yes. I mean, I think there’s a very different history in the UK and the US as far as engagement in clinical trials with African-Americans here, and so I think there are different issues here. But I do think that as more African-American patients are involved in trials, we are starting to see quite a strong group of advocates who are advocating within their community; and that really is the best way to access these patients and for them to partake in trial.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Terrific. Thank you very much, Philip, and thank you, Isabelle. I’d now like to turn the call over to Eric Green.

PRESENTATION

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

Thank you, Barry, and I’d also like to offer my thanks to Dr. Hawkins and to Isabelle for their presentations and perspectives on these two diseases, I think especially Isabelle’s recounting of the one patient’s experience with FAP and the impact that disease had on his family and then ultimately on him.

I will provide a brief overview of our products being developed for the treatment of ATTR amyloidosis and then hand it over to Dr. Jared Gollob, who will review our highlights of our clinical data from each of our two clinical programs.

Turning to slide 42, as has been mentioned earlier, our most advanced development programs are focused on transthyretin-mediated amyloidosis, or ATTR amyloidosis. As Dr. Hawkins has already mentioned, ATTR is an autosomal-dominant inherited disease and we think it affects about 50,000 patients worldwide.

As described thoroughly previously, there are two predominant clinical forms: the polyneuropathy, or FAP; and also cardiomyopathy, what we call FAC. But regardless of the presentation, ATTR is uniformly a progressive, debilitating disease that ultimately leads to an earlier death.

Current treatments in this indication are severely limited, as has been outlined. We feel there is clearly a significant need for new medicines.

ATTR is caused by mutations in a liver-produced protein called transthyretin, where the mutations cause the proteins to misfold and create damage to nerves, the heart, and other tissues. The RNA opportunity in ATTR amyloidosis is to knock down the disease-causing proteins and potentially to halt disease progression.
Next slide. We are developing two separate RNAi therapeutics for ATTR amyloidosis: patisiran and revusiran. Patisiran is our most advanced program, focused on ATTR polyneuropathy, and is delivered by intravenous administration.

There is an ongoing Phase 2 open-label extension, or OLE, study with clinical evaluations scheduled for every six months. We’ve recently announced that we will report complete 12-month data at the ANA meeting in September and expect to present our initial 18-month data at the EU ATTR amyloidosis meeting in early November. The program is also currently enrolling patients in our APOLLO Phase 3 trial, and we have recently initiated dosing in our APOLLO OLE study for those patients that participated in the APOLLO study.

Revisiran is our most advanced subcutaneously administered RNAi therapeutic in the clinic and is focused on ATTR cardiomyopathy. For this program we also have an ongoing Phase 2 OLE study, and we expect to present the first interim results later this year.

The ENDEAVOUR Phase 3 trial of revusiran in FAC is also enrolling, as well as the DISCOVERY screening study. Dr. Gollob will discuss each of these studies in more detail in the next few minutes.

We are also advancing a development candidate for a second generation, which we call ESC-GalNAc-siRNA targeting TTR. Based on the emerging profile of this candidate we expect it to support a once-monthly and possibly a once-quarterly subcutaneous dosing regimen. We plan to share additional details on this program at the OTS meeting in October.

Now I will turn it over to Jared.

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

Great. Thank you, Eric. I’m going to be essentially providing a review of the progress that we’ve made both within our patisiran and revusiran programs to date. Both of these programs are premised on a therapeutic hypothesis that the reduction or inhibition of liver-derived mutant and wild-type TTR by these drugs will lead to a reduction in the amount of unstable circulating TTR tetramers in the blood, which in turn would essentially prevent further deposition of amyloid at various target organs and even over time promote clearance, which would then eventually result in stabilization of neuropathy and cardiomyopathy, and possible eventual recovery as well of both the neuropathy and the cardiomyopathy.

I’m going to be starting with a review of the patisiran program. Within this program we’re seeing very encouraging results emerging from the Phase 2 open-label extension study that’s providing support for this therapeutic hypothesis, which we think bodes well for what we anticipate seeing in the pivotal Phase 3 APOLLO trial.

Moving to slide 45, the Phase 2 study with patisiran was the first study with patisiran in patients. For both the patisiran and revusiran programs we thought it very important to involve patients in the early stages of clinical development, both to engage patients and the clinicians, and also to understand the safety profile of the drug and the potential pharmacodynamic activity and clinical activity of the drug in actual FAP patients.

This Phase 2 study of patisiran was performed in FAP patients, and this study was critical in allowing us to essentially establish the dosing regimen of patisiran to take forward into the Phase 2 open-label extension study as well as the APOLLO Phase 3 study. In short, as shown on this slide, this was a 29-patient study; and this slide is really highlighting the pharmacodynamic effect of the TTR-lowering effect of patisiran based on the dose given to the various groups of patients.

We also were exploring within the study dosing once every three weeks or once every four weeks. In the left panel you can see that a dose of 0.3 milligrams per kilogram gave us TTR knockdown of up to 96%. By using an every three-week dosing schedule, we were able to maintain TTR knockdown of at least 80% from dose to dose.

This was seen in patients both on TTR tetramer stabilizers as well as in patients off tetramer stabilizers. And importantly, in the right-hand panel we saw a similar effect of the drug knocking down both the wild-type and mutant form of TTR in these FAP patients, many of them have the V30Met mutation.
Moving on to the next slide, the patients on the Phase 2 study were eligible to roll over onto the Phase 2 open-label extension study. 27 of those 29 FAP patients did roll onto this study, which uses patisiran at a dose of 0.3 milligram per kilogram every three weeks for up to two years. Importantly, in addition to looking at safety and tolerability and the effect on TTR lowering, there were a number of clinical endpoints in the Phase 2 open-label extension study that are actually the same endpoints as on the APOLO Phase 3 study. So this trial gives us an opportunity to look at the potential activity of TTR lowering, to help us anticipate what we expect to see in the APOLO Phase 3 trial.

We have presented 12 months mNIS+7 patient data on the first 20 patients this past April at the AAN meeting, and we plan to present the full data set on all 27 patients at the ANA meeting coming up at the end of September. We then plan to -- expect to report 18-month data in late 2015.

As noted on this slide, a number of the secondary endpoints included various measurements to assess neuropathy progression over time, including the mNIS+7 composite neurologic impairment score, which is the primary endpoint on the APOLO study, as well as other quality of life and other measures of disability and mobility that are very important in assessing how patients feel and function.

The next several slides provide the data that we shared at the AAN meeting this past spring. This slide shows the baseline demographics of the 27 patients enrolled onto the Phase 2 open-label extension study. There was about a 2-to1 ratio male-to-female, expected for this population. There were a variety of TTR genotypes, the most common being V30Met.

The majority of patients had Stage 1 disease although we did have some patients with more advanced disease. As you can see on this slide, approximately two-thirds of the patients came onto the study already being treated with concurrent tetramer stabilizers, either tafamidis or diflunisal.

At the time of this presentation in April we had administered over 500 doses. The median number of doses given per patient to date was 19. And we had treated patients on average for over one year, with some patients being treated as long as almost 17 months.

Slide 48 provides the safety summary. Here we see that the patisiran dosed at 0.3 milligram per kilogram every three weeks was very well tolerated in this study looking at chronic dosing. You can see there are a limited number of adverse events shown on this table; the most common adverse events seen were flushing, which were mild in severity, and infusion-related reactions, also mild in severity.

There were actually no clinically significant changes seen in liver function tests in any of these patients, in renal function or hematologic parameters. There were no study discontinuations. So essentially, the safety profile was very favorable at the time of this analysis this past April.

Slide 49 looks at the pharmacodynamic data, the TTR-lowering results seen in these patients. Here we’re looking at percent serum TTR knockdown as a function of time for the entire group.

This goes out almost as long as 16 months. What you can see here is that we were able to maintain an average of 80% TTR knockdown over that 16-month period, with an additional average knockdown of close to 88% to 90% in between doses during that same period of time. Importantly, we saw the same degree of knockdown in patients whether they were on patisiran alone or on patisiran in conjunction with TTR tetramer stabilizers.

Now these patients were also followed with regard to the course of their neuropathy. The main measures used for that were the composite Neuropathy Impairment Scores shown on the slide: the mNIS+7 and the NIS.

The mNIS+7, which is the primary endpoint in the APOLO study is particularly well suited to FAP patients as it really measures the totality of the disease in these patients with FAP. It covers both sensory motor neuropathy by measuring motor strength and weakness; it uses an objective measure of sensory neuropathy, the so-called quantitative sensory testing, or QST; and it includes additional objective measures of neuropathy, such as nerve conduction studies and looking at autonomic dysfunction through postural blood pressure.

As you can see on this slide, a higher mNIS+7 score indicates worsening of disease. The maximum number of points or the maximum impairment that a patient can have is 304 points for the mNIS+7.
Slide 51 shows the mNIS+7 results over time in the 20 patients who had 12-month data and the 27 patients who had 6-month data at the time of this presentation at AAN last spring. The mNIS+7 at baseline is shown on the y-axis, and then you can see how that changes for individual patients: each line is an individual patient over time looking at the score at baseline, 6 months, and 12 months.

What's really striking here is that if we look at the change from baseline to month 12 you see on average a 2.5 decrease or improvement in the mNIS+7 score, with a median change of minus 1.5, also showing improvement. If we look at all the various components of the mNIS+7, these are all tracking in the same direction, either showing improvement or stability.

As you can see on the graph itself, this favorable impact of the drug is seen regardless of where patients start. So even patients with higher mNIS+7 score, indicating greater severity of neuropathy, appear to be achieving benefit.

So essentially on this particular slide looking at mNIS+7, we essentially are seeing a halting of neuropathy progression at both 6 and 12 months in the patients who are receiving patisiran. And we were able to see a similar impact both in patients who are on patisiran alone as well as in patients who are on patisiran in addition to TTR tetramer stabilizers.

Slide 52 shows a table which allows us to contextualize the results that we're seeing in the 2 open-label extension study. In the far right column on this table, you can see the results at 12 months for mNIS+7 change and NIS change on the Phase 2 open-label extension study, showing a minus 2.5 or a 0.4 change at 12 months. This compares very favorably to what we've seen in a natural history study that we performed in collaboration with five different sites in 283 patients, where you can see that in these untreated FAP patients we would have expected a 14- to 18-point increase in NIS or mNIS+7 at one year.

If we look at two clinical trials, the tafamidis Phase 2 study in non-V30Met patients and the diflunisal Phase 3 study, and you look at those patients who are not receiving drug, you can also see that we would have expected a 13- to 17-point increase in mNIS+7 and a 10- to 14-point increase in NIS (sic - see slide 52, "NIS") at 12 months, which represents an incredible degree of progression in neuropathy impairment.

Even in those treated with drug we're still seeing a 5- to 7-point increase in mNIS+7 and a 4 to 5 increase in NIS. So even in drug-treated patients on these studies we're seeing significant neuropathy progression, whereas in the Phase 2 open-label study with patisiran we're essentially seeing either improvement or no progression, again providing evidence, we think, that we're seeing halting of neuropathy progression in this patient population.

Slide 53 essentially summarizes these results. Essentially patisiran was generally well tolerated in FAP patients out to 17 months. We were able to see a robust, sustained mean serum TTR knockdown of approximately 80%, with further knockdown between doses of close to 90% looking out for approximately 16 months.

The Neuropathy Impairment Scores were stable through 12 months. This compared very favorably to the other published studies, and this favorable effect was seen in patients with or without concurrent tetramer stabilizers. So in aggregate we think that these results are consistent with the therapeutic hypothesis that TTR knockdown does have the potential to halt neuropathy progression.

Slide 54 is presenting the APOLLO Phase 3 study design. This is an ongoing study that is open to patients with any FAP TTR mutation and includes patients with Stages 1 and 2 disease.

It allows for a broad range of neuropathy severity on study entry, with a baseline NIS score of 5 to 130. Although patients can be on prior tetramer stabilizers, they must come off these stabilizers at the time of entry onto the study.

The study design involves 2-to-1 randomization of patisiran given at 0.3 milligram per kilogram every three weeks versus placebo. The primary endpoint is mNIS+7 at 18 months; and the secondary endpoints include the Norfolk Quality of Life and other important measures of how patients feel and function, including NIS-weakness, modified body mass index, the 10-meter walk test, and a measure of autonomic dysfunction called the COMPASS-31, in addition to a number of other important exploratory endpoints.
With regard to statistical considerations, essentially these were based on the estimated rate of neuropathy progression in the placebo arm; that is based on the natural history data that I just reviewed. Our study has 90% power to detect as little as a 37.5% difference in the change in mNIS+7 between the two treatment groups.

The study includes a blinded interim analysis of variance for sample size adjustment. There’s also a potential interim analysis for efficacy that is under consideration, given the promising results that we're seeing in the Phase 2 open-label extension study; and here regulatory discussions are pending.

Turning now to the revusiran program, slide 55 shows that revusiran is a GalNAc-siRNA conjugate in which a triantennary GalNAc moiety is covalently linked to the sense strand of the RNA duplex of the siRNA targeting TTR. The GalNAc essentially allows for targeting to the liver, specifically targeting to hepatocytes that express the receptor for GalNAc, which is the asialoglycoprotein receptor, such that once the receptor is engaged by the GalNAc moiety, the siRNA is internalized into the cell, released into the cytoplasm where it can then engage the RNAi machinery to knock down the target of interest.

Revisiran was essentially our first GalNAc-siRNA conjugate using our standard template chemistry. We now also have the enhanced stabilization chemistry that is used for all programs after revisiran that has significantly improved potency and durability.

Slide 56 provides a summary of the nonclinical safety seen with revisiran. These studies were performed both in rat and in nonhuman primate. Very little was seen in the way of target organ toxicity in either of these species.

In the rat, in the 6-week study very minimal adverse events were seen in the liver of these animals that were transient and seen only at high doses. When the rats were treated again for 6 months there were no new target organ pathologies identified. We did observe transient nonadverse edema seen at injection sites at high doses of 100 milligrams per kilogram.

In the non-human primate this was also a very clean set of studies. No target organs of toxicity were identified in a 6-week study. The 9-month study also did not see any target organs of toxicity, and the no observable adverse event level was greater than or equal to the highest dose tested of 200 milligrams per kilogram.

Here in the monkey we did also transient, non-adverse edema at the injection site at the high dose of 200 milligrams per kilogram. So overall, a very favorable preclinical safety profile.

The first study of revusiran in humans, which is really the study that provided our first human proof-of-concept with the GalNAc-siRNA conjugate was a Phase 1 study in healthy volunteers as shown on this slide. Here we dosed healthy volunteers on a mg-per-kg basis with increasing doses of revusiran.

As you can see, we saw a robust dose-dependent knockdown of serum TTR up to 95%. At doses of 5 milligram per kilogram or greater, we saw more than 85% mean TTR knockdown that was durable.

I should note on this slide, you can see at the bottom of the slide that the dosing regimen used on this Phase 1 study was to give revisiran as five daily doses during the loading phase, followed by five weekly doses. So a total of 10 doses given over 35 days.

Having established the pharmacodynamic activity of revusiran in healthy volunteers, we then moved on to study the safety and activity in patients, specifically in TTR cardiac amyloidosis patients including FAC as well as SSA or wild-type patients, and the Phase 2 study design is shown here. We used the same dosing regimen that we used in Phase 1: five daily doses followed by five weekly doses.

There were two dose groups, 5 milligram per kilogram as well as 7.5 milligram per kilogram. The objectives here were to evaluate safety and the TTR-lowering effect of revusiran. We also did include exploratory clinical measurements relevant to this population that were performed on days 42 and day 90 after dosing was completed on day 35.
On slide 59, this table shows the baseline demographics for the 26 patients enrolled onto the study. 14 of these had FAC; 12 had SSA.

In the FAC population, you can see there were a variety of mutations, the most common being the T60Ala and the V122I mutations that Dr. Hawkins referred to in his presentation. All of the SSA patients, of course, had wild-type TTR. Most of these patients were NYHA Class 2 with a good performance status, and only a small number of these patients were on a concurrent tetramer stabilizer, namely diflunisal.

The safety results for the study that were presented at the ACC Annual Meeting earlier this year are shown on slide 60. As you can see, there was a very favorable safety profile. All the related treatment-emergent adverse events were mild in severity.

We saw injection site reactions in only 15% of patients, including erythema in three and rash in one. We saw only transient mild liver function test changes in three of four patients; these were less than 1.5 times the upper limit of normal for one of the transaminases, the ALT, which didn't lead to any dosing interruption.

There was one possibly related serious adverse event for an LFT change that was approximately 4 times above the upper limit of normal for the transaminases. But this resolved with continued dosing and was overall graded mild in severity. There were no study discontinuations and importantly no significant changes in renal function, other laboratory abnormalities, or any hematologic parameters.

If we move to slide 61, we now see the TTR lowering data shown by dose group: so 23 subjects on 5 milligram per kilogram; three on 7.5 milligram per kilogram. We saw very comparable TTR lowering across both of these dose groups, with maximal TTR lowering in the 98% range and mean TTR lowering in the 85% to 92% range for these dose groups.

So very robust TTR lowering seen in both FAC and SSA patients. Although not shown on this graph, we did see really equivalent TTR lowering in both of those populations of TTR cardiac amyloidosis patients.

Many of these patients that were on Phase 2 have rolled over onto an open-label extension steady. Just as we have an open-label extension study for patisiran, a similar principle here for revusiran to allow us to further assess safety and pharmacodynamic activity with chronic dosing and to allow us to start to look at clinical activity of the drug with various measures of cardiomyopathy.

Essentially, patients coming onto the Phase 2 open-label extension study receive a fixed subcutaneous dose of 500 milligrams. It's given daily times five for the loading dose and then it's given weekly for up to two years.

Again, the primary endpoints are safety and looking at TTR lowering, as well as additional exploratory clinical endpoints that we're evaluating every 6 months. Many of these endpoints line up with the endpoints that are on ENDEAVOUR Phase 3 study. These include looking at 6-minute walk distance, cardiac imaging to assess cardiac amyloid burden and function, as well as other measures relevant to this population.

25 of the 26 patients rolled over from Phase 2 onto this open-label extension study. We expect to report initial 6-month data on approximately 15 patients toward the end of this year.

As in Phase 2, revusiran has been generally well tolerated in the majority of these patients. We reported earlier this month that there were three patients who discontinued due to injection site reactions, so-called ISRs, including some with associated diffuse rash. These injection site reactions are expected adverse events essentially with any drug that's administered subcutaneously, including patients receiving oligonucleotides.

Slide 63 is essentially providing perspective on what has been seen with regard to injection site reactions in patients treated with antisense oligonucleotides with two different drugs, mipomersen and drisapersen. Both of these drugs are administered weekly by subcutaneous injection.

For mipomersen, the pooled Phase 3 experience in patients with hyperlipidemia — and there have been over 260 patients in that experience — revealed that ISRs were seen in 84% of patients, most of them being mild to moderate in severity, although some were severe, and most common symptoms including what one would expect to see from local reactions, such as erythema, pain, swelling, and discoloration.
A similar high rate of ISRs were seen in the Phase 2 experience in Duchenne muscular dystrophy with drisapersen in a study of 35 patients. The ISR rate was 78% to 88% with weekly dosing. All events there were mild to moderate in severity; and the most common signs and symptoms were fairly similar to what was seen with mipomersen. So this experience essentially helps, we believe, to put the revusiran experience in perspective with regard to the sorts of events that can be seen with oligonucleotides when they're administered by subcutaneous injection.

Slide 64 reviews the ENDEAVOUR Phase 3 study design. The ENDEAVOUR Phase 3 trial is being performed in patients with FAC. To be eligible for the study, patients have to have a documented TTR mutation, evidence for amyloid deposits on biopsy, a history of heart failure, and evidence of cardiac amyloid involvement by echocardiogram. Patients here are randomized 2-to-1 to receive revusiran, given 500 milligrams subcu daily times five, followed by weekly for 18 months; or to placebo given on the same schedule.

The co-primary endpoints include the change in 6-minute walk distance at 18 months compared to baseline and the percent reduction in serum TTR over 18 months. And the secondary endpoints shown here include composite CV mortality or cardiovascular mortality in hospitalization, change in NYHA class, and change in a quality-of-life measure called the KCCQ.

The 6-minute walk distance was chosen in part because the natural history data that we've analyzed in FAP patients showed a substantial decline of 140 meters over 18 months, therefore indicating that in the placebo arm of this study we should see a similar rapid decline in the 6-minute walk distance, which provides an ideal opportunity for us to be able to look at the impact of revusiran on that decrement in 6-minute walk distance. The study has a 90% power to detect as little as a 39% difference in the 18-month change from baseline 6-minute walk distance between the treatment groups, with a significance level of p less than 0.05. The study does include an unblinded interim analysis for futility when approximately 50% of patients reach 18 months.

Slide 65 just shows some of the natural history data that I just alluded to. These are natural history data in 39 FAC patients with a V122I mutation from the National Amyloidosis Centre. These data are from Dr. Philip Hawkins and his group.

As you can see, when you're looking at the change from baseline in 6-minute walk distance, either as an absolute change in meters on the left or a percent change from baseline, you can see that there's a substantial decrement over a relatively short period of time, 18 months, in the 6-minute walk distance: an approximate 140-meter decline corresponding to about a 46% decline from baseline. So just as in SAP where the rapid rate of neuropathy progression provides us an ideal situation for assessing the impact of patisiran in TTR lowering on the progression of neuropathy, here in patients with FAC using 6-minute walk distance as a primary endpoint, this provides another ideal opportunity to show the potential impact of our drug on this important measure of function in these patients with cardiomyopathy that changes fairly rapidly over an 18-month period.

Then finally, another important component of the revusiran program is the DISCOVERY screening protocol. The rationale for this screening study is to allow us to determine the frequency of TTR mutations in subjects who are suspected of having cardiac amyloidosis. Importantly, subjects who are diagnosed with FAC through the study may then be eligible for enrollment onto the Phase 3 ENDEAVOUR trial.

The study plans to have 75 sites and to enroll up to 1,500 patients. Essentially, on this study patients with heart failure who are suspected to have cardiac amyloidosis -- because they have two or more of the following criteria shown on the slide -- will have sequencing of their TTR gene. Those patients who have a positive pathogenic mutation, they will then have a further medical history provided from the prior 12 months, an echocardiogram, as well as cardiac biomarkers measured through a blood test. They will also have the option of having a tissue biopsy done to look for amyloid deposits and to undergo a 6-minute walk test.

We think this screening study will be very important in helping us understand the frequency of TTR mutations in individuals suspected of having the disease and also potentially provide a source of newly diagnosed patients who may then be eligible to be treated on any clinical trial, including the ENDEAVOUR Phase 3 study.

And with that, I will turn it over to Eric for the remaining several slides.
Eric Green - Alnylam Pharmaceuticals, Inc. - VP General Manager TTR Program

Thank you, Jared. On slide 67, just briefly, in summary we are developing patisiran for the treatment of FAP. The Phase 2 OLE study has provided some evidence of potential halting of neuropathy progression at 12 months and with a favorable safety profile to date. The APOLLO study is progressing and, if positive, should enable an NDA submission in the 2017 time frame.

Revasiran is a subcutaneous drug being developed for FAC. In addition to the ongoing Phase 2 OLE study we also have the DISCOVERY screening study and our Phase 3 ENDEAVOUR study, both of which are currently enrolling patients.

Excitingly, the ALN-TTRsc02 is a second-generation GalNAc conjugate targeting TTR that may provide a very favorable dosing regimen for ATTR amyloidosis patients.

Finally on slide 68 we just highlight some upcoming events where we have planned presentations in each of the months of September and October, at the OTS meeting where we’ll talk more about the ALN-TTRsc02 program, as well as in November. With that, I’ll turn it over to Barry for any questions.

QUESTIONS AND ANSWERS

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Thanks, Eric, and thanks, Jared, for that tremendous overview of the Alnylam ATTR program. I'm now going to turn to some questions.

The first question is: How do the Phase 2 open-label extension data impact the likelihood that you'll successfully hit your endpoint in the APOLLO Phase 3 trial?

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

While it’s still somewhat early and these data are coming from an open-label study, these results do give us increased confidence that our ongoing APOLLO Phase 3 study of patisiran has the potential to show a significant difference in the change in mNIS+7 between the patisiran-treated and placebo-treated groups.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Great. A follow-on to that is: When you look at these data, how do they impact the thinking around expedited regulatory strategy for patisiran? What more can you tell us about potential interim analysis?

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

Well, we do plan to update FDA and EMA with these and any future results at the appropriate time as they are important to the development path of patisiran. These interactions could include a discussion of a possible interim analysis for efficacy in the APOLLO Phase 3 study.

We will provide an update on FDA and EMA interactions when appropriate. But we continue to be very focused on our Phase 3 APOLLO trial and being prepared for a 2017 NDA.
Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Great. How is competition impacting enrollment across the two trials? With stabilizers on the market and Isis/Glaxo also enrolling for FAP, how do you think about trial accrual? And then what’s your competitive commercial thoughts?

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

Well, we are confident that we'll be able to accrue patients, really for a number of reasons. We really over the years have established a very broad network of key opinion leaders and relationships with patient advocacy groups in multiple different parts of the world, and we think this has been very important.

Essentially, our KOL network spans five continents and has been building for greater than five years now. That was one of the reasons why we thought it was important to engage patients and physicians very early in the development program for patisiran.

We have over 30 sites in more than 10 countries that are now open and active. And really through our various outreach activities with investigators and with advocacy groups, awareness of our trial is growing. Many of these sites are really very excited about our science and the data and are eager to work with us.

Also, given the increasing awareness of TTR amyloidosis in the medical community, we are identifying countries and sites that were not previously approached by other companies and by other sponsors. So I think we’re feeling very good about our ability to accrue to APOLLO based on our global fingerprint and our relationships with investigators and with advocacy groups.

I think given the promising results we’re seeing in the Phase 2 open-label extension study and what we anticipate to see with APOLLO, I think we should be very, very competitive even if there are other drugs on the market as well.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Eric, you want to talk about the commercial side of the world?

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

Yes. As we look forward a couple years as our development program concludes and to a submission we hope and expect approval. It will be a somewhat crowded space for a very rare disease.

As mentioned previously, stabilizers are used in some regions of the world. In one instance, a generic product is available in some areas. And another branded product that’s only available in Europe currently and prefer -- what Dr. Hawkins said earlier -- not a substantial amount of efficacy seen with those agents, especially in the cardiomyopathy.

I do believe that our programs -- and we have now talked about two that are in late-stage clinical development, but also the third that we have mentioned as a new development candidate -- does show our commitment to this space, to these patients, and to the treatment of ATTR amyloidosis. I believe we have very competitive product profiles, as we have been able to see through our open-label extension studies, showing the effects on clinical outcomes already with patisiran; and we expect to be able to share that data with revusiran later this fall.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Great, thank you. Another follow-up question I guess on the competitive landscape: Where do you rank your ability to get approval in FAP relative to Isis? It looks like you’re ahead on FAC and they haven’t started trial. What are your thoughts there?
Eric Green - Alnylam Pharmaceuticals, Inc. - VP General Manager TTR Program

In FAP, it's always hard to -- and should never compare two agents that aren't studied in a head-to-head study. Isis has not been able to present much of their clinical data given that they jumped straight to a Phase 3. They have recently announced some data from their open-label extension study, but it's not yet able to make any even relative comparisons to those products.

In FAC, yes, we have started our ENDEAVOUR Phase 3 study. We announced that study started late last year. Isis and GSK guide that they will start their FAC sometime later this year; so we do have an advantage there.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Great. Let's turn to some revusiran questions: Can you elaborate on the ISRs and discontinuations in the Phase 2 OLE study for revusiran?

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

Yes. In terms of the discontinuations that were seen, as mentioned, there were a total of three different discontinuations seen on the revusiran Phase 2 open-label extension study. None of these were serious adverse events.

Two of these discontinuations were in the setting of there being a rash; meaning it was a cutaneous event that was outside of the actual injection site. One of these was mild and one of these was severe.

But none of these events were associated with flulike symptoms or antidrug antibodies or any attenuation of TTR lowering. So overall, the safety profile that we're seeing in the open-label extension study continues to be very favorable.

The decision for a physician to discontinue a patient based on injection site reactions is really an individual decision based on the physician's judgment. But we are encouraged so far by the overall safety profile that we're seeing. And we plan to present interim 6-month data on approximately 15 patients on the open-label extension study toward the end of this year.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Great. I guess given the severity of the patient population and those discontinuations, how do you feel about the powering of ENDEAVOUR? And a follow-up question that is: Did the agencies agree to the 6-minute walk endpoint?

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

In terms of being able to keep patients on ENDEAVOUR to make sure we're adequately powered, certainly the N of 200 that we essentially estimated for the patient population for ENDEAVOUR was based on the possibility of there being dropouts, for a variety of different reasons. We know that patients with FAC who can have moderate to severe disease may come off just from disease progression or for other reasons that have nothing to do with adverse events.

We think overall, based on what we're seeing so far in the Phase 2 open-label extension study, a large majority of patients will be able to probably stay on the ENDEAVOUR trial. But we have planned for the potential for there being some fraction of discontinuations, just as we had the same sort of planning for the APOLLO Phase 3 study.

And the second question, Barry, was --?
Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

The 6-minute walk.

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

Oh, the 6-minute walk distance. Yes, so we actually did have extensive discussions with both FDA and EMA around the 6-minute walk distance as our co-primary endpoint. They were very supportive of that endpoint given the compelling natural history data that we had in the FAC patients, showing that significant decline over 18 months.

So I think the fact the 6-minute walk distance has been, in some studies, associated with even other clinical outcomes such as quality of life and hospitalization, that the agencies to believe that this is a clinically meaningful endpoint, and it is an important measure of function in these patients with cardiomyopathy, and therefore would view it as a very acceptable endpoint, especially for this particular indication.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Great, thank you. You are developing three different programs: patisiran for FAP, revusiran for FAC, and then TTRsc02. I guess a question to Eric: How do you see the three programs playing out commercially?

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

Well, in part it’s based on the timing. Patisiran is our most advanced program; it is in the middle of our Phase 3 enrollment, and at the current pace is likely to be the first onto the market for FAP. Revusiran, since it also is now in Phase 3 enrollment, and we initiated that study late part of 2014, also will likely be the first subcutaneous RNAi therapeutic to be on the market for FAC.

How and when we roll in the ALN-TTRsc02 is still a lot of discussions, one to be followed by obviously clinical data as we generate that, and future discussions with regulatory agencies.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Great, thank you. Are you planning on running a separate study in SSA patients?

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

We certainly are very interested in the SSA population and, as we showed in the Phase 2 study, that included both FAC and SSA. We thought it made sense to focus the Phase 3 ENDEAVOUR study on a genetically defined population, the FAC population; but we are interested in pursuing development in SSA and are at this point actively pursuing various options in conjunction with our investigators. We will certainly provide more information on that in the coming months.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Great. I guess another follow-up question for TTRsc02: Can you tell us more about your timing for bringing it forward?

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

For sc02, for the ESC GalNAc, we will provide additional details at the OTS meeting in October.
Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Okay, great. I would like to turn it now to Josh for the wrap-up.

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

All right. Thanks, everyone, and thank you all for joining us today. This concludes today’s RNAi Roundtable. 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 on Tuesday, September 8 at 9:00 AM Eastern Time as we discuss our ALN-GO1 program in development for the treatment of primary hyperoxaluria Type 1, and in the weeks that follow on the topics listed here on slide 70. Thanks, everyone. Have a great day.

Barry Greene - Alnylam Pharmaceuticals, Inc. - President, COO

Thank you.

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