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ALNY - 2018 RNAi Roundtable: Patisiran & ALN-TTRsc02, for the Treatment of Transthyretin-Mediated Amyloidosis

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PRESENTATION

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

Thank you for joining us for today's RNAi Roundtable, where we'll be discussing ONPATTRO and ALN-TTRsc02 for the treatment of ATTR amyloidosis. I'm Christine Lindenboom, Vice President of Investor Relations and Corporate Communications at Alnylam. With me today are Eric Green, Vice President and General Manager of our TTR program; Dr. Michael Sherman, Chief Medical Officer and Senior Vice President for Health Services in Harvard Pilgrim Health Care; and Rena Denoncourt, Program Leader of our ALN-TTRsc02 program.

Today's RNAi Roundtable is the last in a series of roundtables that we held over the course of the summer. Today's event is expected to run for about 1 hour. Eric will moderate a Q&A session at the conclusion of the presentation. If you'd like to submit a question, you can do so at any time during the event by typing your question in the Ask A Question field. Please note, we will not be discussing ONPATTRO's launch performance on today's roundtable.

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

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

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

Excellent. Thank you, and thanks, everyone, for joining us today to hear about our TTR programs. As all of you know, Alnylam is the industry leader in RNAi therapeutics, which represents a whole new class of innovative medicines. RNAi is a powerful approach for gene-silencing that harnesses a natural and catalytic mechanism. Through Alnylam's efforts, RNAi is a clinically proven approach that has resulted in an approved product, ONPATTRO.

Alnylam has developed a pipeline of products targeting different liver express proteins. We have demonstrated human proof of concept with 7 products, including 3 programs that are in late-stage development and 1 that is now commercial. Importantly, we have retained global rights to most of these programs. Today, we will focus on our TTR programs with most of our time focused on ONPATTRO, or patisiran, and Rena will provide an update on ALN-TTRsc02 in a little bit.

As a reminder, hereditary ATTR amyloidosis occurs in people with inherited mutations in the TTR gene, and we use a deposition of mix-folded TTR protein as amyloid in various different tissues throughout the body. This is a multi-systemic disease, resulting in intractable peripheral sensory polyneuropathy, autonomic neuropathy and/or cardiomyopathy as well as other disease manifestations. Common estimates for the global prevalence assume approximately 50,000 patients, but only a small percent of the disease are likely diagnosed.

Not shown on this slide, wild-type ATTR amyloidosis is a non-hereditary progressive disease of undefined ideology that occurs when mix-folded TTR proteins accumulate as amyloid deposits in multiple organs, including the heart, resulting predominantly in cardiomyopathy. The prevalence of wild-type ATTR is uncertain, but many key opinion leaders believe there are many multiples more wild type than hereditary patients.

As we shift to talk about ONPATTRO in the next few slides, it is important to note that ONPATTRO has only been studied in the hereditary form of the disease to date. With ONPATTRO's approval in early August, the first ever RNAi therapeutic was approved, heralding the arrival of an entirely new class of medicines. In the U.S., ONPATTRO is the first and only therapy approved for patients with hereditary ATTR amyloidosis. Specifically, ONPATTRO is approved for the treatment of the polyneuropathy of hATTR cancer amyloidosis in adults. Through extensive planning and preparation, ONPATTRO was on the market the first business day after the FDA approval. This meant ONPATTRO, as you can see on the picture in the slide, was available at our third-party logistics provider. And we were in a position to process a patient start form, ship product to a customer that ordered it, collect revenue from that order and promote and engage with all the stakeholders with excellence and integrity.

On Slide 12, you can see some additional information from the U.S. label. As was done in APOLLO, the randomized Phase III study that supported ONPATTRO's approval, patients are dosed at 0.3 milligrams per kilogram once every 3 weeks if the patient is less than 100 kilograms. In addition, they receive pre-medications on the day of infusion. Importantly, there are no contraindications in the label, and infusion-related reactions are noted in the warnings precautions as well as the need for Vitamin A supplementation. Common adverse event reactions noted in the label are upper respiratory tract infections as well as the infusion-related reactions we just mentioned. And no required laboratory monitoring is needed.

There are a lot more information on ONPATTRO. You can obviously always go to find the full prescribing information that's available on onpattro.com or by following the link that's on this slide in the bottom.

The primary endpoint for APOLLO was a difference between patisiran and placebo in change from baseline in mNIS+7. The chart on Slide 13 as well as in the U.S. package insert shows the difference of 34 points after 18 months of treatment in APOLLO between the 2 treatment arms. The ONPATTRO-treated patients showed a mean change of minus 6 points. That is an improvement in neuropathy impairment over 18 months. In addition, over half of the patients treated with ONPATTRO experienced a reversal in neuropathy impairment and define that as a change in mNIS+7 at 18 months of less than 0 compared to 4% of placebo patients.

Similarly, on Slide 14, you can see that ONPATTRO demonstrated significant improvement in the quality of life versus placebo here, as measured by the Norfolk Quality of Life measure after 18 months of treatment in APOLLO, with a 21.1-point difference between the 2 arms. Indeed, just over 50% of ONPATTRO-treated patients experienced improvement. That is a change less than 0 at 18 months from baseline and quality of life compared to 10% of placebo-treated patients. As with mNIS+7 on the previous slide, the mean change from baseline was negative as early as 9 months, which was the first efficacy assessment in APOLLO, and already showed a substantial separation from those patients on placebo arm.

As we have discussed the APOLLO results numerous times in other forms, we won't go any more in depth in those results. But I do note that the full result of the APOLLO study were published in the New England Journal of Medicine earlier in July of this year. Excitingly, this is the second time patisiran has been in the New England Journal. The first was back in August 2013 when the Phase I results were also published in the journal.

In the U.S., we are actively launching ONPATTRO after several years of preparation. Our activities are aligned within 3 main areas, as shown on the slide: increasing awareness and driving diagnosis of hereditary ATTR amyloidosis, educating physicians about ONPATTRO and providing a compelling story to drive brand choice, and providing an optimized patient experience for those who choose to take ONPATTRO. For disease awareness, we've had our physician-focused and our patient-focused disease state awareness websites live for over 1.5 years now. And those are in the slides here. The bridge is the patient-focused site, and the hereditary ATTR amyloidosis with a red circle is our physician-focused disease state.

Diving a little deeper into the first bucket of disease awareness and diagnosis. Alnylam Act is a free of charge, third-party genetic testing and counseling program. This program is intended to reduce barriers to genetic testing and counseling to help people make more informed decisions about their health. In the U.S., both genetic testing and counseling services are available. And in Canada, genetic testing is available. Physicians can learn more about this program from the website, with a link on this slide shown here.

In the third bucket, once a patient and their physician has decided to take ONPATTRO, Alnylam assists as a comprehensive program dedicated to helping guide patients to treatment with ONPATTRO. A dedicated in-house case manager can provide personalized support throughout the treatment process with examples of such support shown here on Slide 18. Again, without wanting to go into all the details, additional information can be found at the website listed at the bottom of the slide.

Switching to Europe. We were excited to announce just under 2 weeks ago that the European Commission had granted marketing authorization for ONPATTRO. In the EU, ONPATTRO is indicated for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. The label includes data from the primary endpoint, again, this was the mNIS+7; all secondary endpoints; as well as data from exploratory cardiac endpoints. For the full review of the EU label for ONPATTRO, please see the summary of product characteristics, or SMPC, from the link on the slide or, again, by going to onpattro.eu for a quick link in the upper right-hand corner.

We will be launching across the European Union over the next weeks and months, most likely first in Germany. We are translating all necessary materials, such as the vial and carton labels, to enable ONPATTRO to be supplied to customers as well as filing any necessary health technology assessment commissions across the various countries.

As in the United States, and really around the world, raising awareness of this disease is critical in Europe. And both of our disease state education campaigns, again, for patients and for physicians, have been translated into local languages in our key markets. And as we launch in each country, our commercial branding will become more prevalent and evident also.

And finally, a brief update on other parts of the world. In the U.K., patisiran was approved for inclusion in the Early Access to Medicines Scheme, or EAMS, for use in patients with hereditary ATTR amyloidosis. In Japan, we have hired a regional head of Asia and already brought on a very strong senior leadership team. And we remain on track to file our JNDA in mid-2018, which, assuming a positive review, would lead to an anticipated approval some time in mid-2019 or hopefully June 2019. We also have anticipated regulatory submissions in Canada and Switzerland later this year yet, and we continue to build our infrastructure to support the commercialization in those regions and elsewhere in the world throughout 2019 and beyond.

Please remember to submit your questions. But at this time, I think we will hold any questions on ONPATTRO until the end of the session, so that we can move to our guest speaker. So with that, I'd like to welcome Dr. Sherman to speak about his perspectives as a key player in the U.S. health care market. Dr. Sherman is the Chief Medical Officer and Senior Vice President for Health Services at Harvard Pilgrim Health Care. Michael?

Michael Scott Sherman - *Harvard Pilgrim Health Care Inc. - Chief Medical Officer and SVP*

Yes, well, again, thank you for that introduction. And it's actually exciting to be a part of this. Payers are understandably concerned about rising cost of health care from all perspectives, all of the expenditures that go on. But it is always exciting to see therapies for unmet needs. And our litmus test as a payer really is what are the kinds of care that we would want to be made available for ourselves and members of our family. And again, since we do insure ourselves and we live by our policies, we actually do eat at our own kitchen, and we do believe that. And certainly, if you look at the therapy, the unmet need, the information you saw about what happens to people who aren't treated, it's hard to argue that we shouldn't look to make patisiran ONPATTRO available to our members.

Now the environment that we're in is difficult. We actually, as a payer, I think we're a well-functioning payer, but we've actually had financial losses for several years and we're just coming out of them this year. And when costs go up, we're kind of in this place. We're between a rock and a hard place. On the one hand, our stakeholders want the right therapies available for themselves. Generally, most of our customers are employees, although we have some Medicare Advantage in exchange as well. So they want the drugs available for their employees in most cases, yet we get a significant pushback when costs go up. And if you think about it, when costs go up for drugs, we have -- or frankly, for anything, we have 3 levers we can pull. One of them would be to raise the cost share. And if you think about the cost of some of these drugs, raising cost share clearly isn't a viable option. And I'd also point out that there are some maximums that can be paid out of pocket under the Affordable Care Act, which for a family would be a little under $15,000. So that's clearly not something we can do.

Second, you can raise the deductible. But we know people already are very angry about that. And frankly, raising deductible a thousand or 2 won't help or we can raise premiums. So generally, when you look at how you manage all of the high-cost therapies, I think it's all about the premium. And we know that there's pushback on that. So our goal is to make sure that we're balancing that access and affordability. And one way to do that is to make sure that we're doing a better job of paying for value. And my own feeling is that while we -- we, of course, always will have policies and restrictions ultimately. And I'm speaking not just about pharmaceuticals, but across the entire spectrum. Most of us believe that paying fee-for-service

is not a good formula for success to risk -- to get high quality, high-value care. And most of the rest of our health care delivery systems actually move toward paying for value. And in fact, on the provider side, about 3/4 of our physicians are in some flavor of a value-based agreement.

So the idea of moving from that area to pharmaceuticals and even diagnostics, where we've done some work, frankly, seems like common sense.

On the other hand, it's hard to deal with a unique health -- good partners. If you -- one of the things about where we've been, and let me talk about that in contrast where I think we need to go, we've done over 15 value-based agreements for a number of drugs across the board, ranging from some of the diabetic drugs to cardiovascular, to drugs for heart diseases to gene therapy. And my own sense is that the ones we're doing for the traditional areas, nonspecialty drugs like with diabetes, are interesting. And I think I can check off the box if we've got proof of concept. Maybe there's been some dollars saved, but I don't think that really is the area to focus. I don't know that that's going to move the needle sufficiently.

To me, the area we need to focus in are where you've got an unmet need, a fairly high cost for the therapy and some variable degree of response. And that's where you range your situation where, as a payer or even just as a physician, I think it's easy to agree that you want to make these therapies available. And then although we can debate what the cost should be, if it works, it's certainly worth a lot, particularly to the people receiving the drug, which, is frankly, the most important person. On the other hand, the higher the cost, the more that one would argue that it's not worth it when it's not effective. And so the question has been, how do you reconcile those 2? How do you make it a situation certainly for the payers, which can be either be barriers or facilitators? How do you make it a situation where it becomes heads, you win; tails, you don't lose?

And for that reason, I think focusing more on rare diseases, on the gene therapies, even on cancer, where you do have those high cost and variable outcomes and where we think that we really can use this model to make a difference and help ensure that we make these therapies available to the beneficiaries. With Alnylam, again, very interesting here and a little bit different in that they actually approached me, I think it was probably a year, maybe a little bit more, before the drug was approved. And there were a couple of reasons for that. One is that I've known some of the executives and senior people at Alnylam for some time. And frankly, I have a lot of respect for them for their integrity, for their caring and for their thoughtfulness.

And so although I think it's hard to say payers will say, "Come to us early." Sometimes, it can be hard to get share of mind because everyone's busy. But when they reached out, based on that existing relationship, I was happy to sit down and meet with them. And quite frankly, it was very much a blue-sky type of discussion. They came to us with the idea that they want to do some thing value-based. But again, it's a new drug. When you're talking about something which has hard endpoints like reduction in admission or a hemoglobin amyloid C, it's easier to do. But in this type of situation with the neurologic disorders, it's fairly complicated. So frankly, it required a lot of sitting down together, a lot of brainstorming and thinking collaboratively. And I've always been somewhat amused that when you read the newspapers and you see the finger pointing, whether it's the PBMs in pharma or payers, et cetera, it sounds like it's somewhat a bit of a snake pit. But when you sit down one-on-one with individuals like the people from Alnylam, like others whom I've collaborated with, you quickly get to a point where you realize they care about the same things, which are getting the right drugs to the right people at the right time. And I always find myself having more respect for the people I'm working with.

So over a period of time, we went through different scenarios to talk about what an agreement might look like, brainstormed over endpoints, et cetera. And at the end of the day, we did come up with something. And I won't get into a lot of detail on it, but I'll say that it's got a component for suboptimal responder. So if someone does not respond as we would hope, effectively, the price goes down through a rebate mechanism. And then there's another piece where if the individual under certain circumstances goes on to acquire a liver transplant as a consequence of the disease, and there's some caveats that are obvious, like they should be on transplant list beforehand, Alnylam would pay for a portion of that up to a cap. So again, I think those are the right things to do to help align outcomes and value. And I think, frankly, it sends a positive message to outside stakeholders that they are committed to do the same thing.

And I'd also say that from the pharma companies' perspective, and I won't speak for Alnylam, but I'll speak a little bit for the industry because I have a lot of discussion, I know that there's a lot of concern about even the inspector of regulation and concerns in others. And I think to the extent that companies can show that they're doing the right things, having the discussions and working to drive outcomes, agreements or pricing, where the price data is commensurate with the value delivered to the patient, I think that provides a certain amount of defense against those kind of tailwinds, I guess -- or headwinds, I should say.

The other thing I'll point out is that -- and this is something we end up in a lot of debates about. I mean, a lot of the health care dollar goes toward drugs. And in fact, people debate what it is and it's different perhaps from the Medicare to the commercial population. But we actually looked at what we stand on a commercial population. And we found that one out of every $4, if you look at the medical and the pharmacy benefit drugs, 25% of what a commercial payer spends goes to our drugs. And that doesn't even include what is spent in the hospital setting since those are generally buried within DRGs. And we don't have visibility. So it's actually higher than that.

Now the bigger question is, is that a good number or a bad number? And I submit it's a number. It's neither good nor bad. But to the extent that we have therapies that are making that number go up, that keep people alive longer, that keep them out of the hospital, that provide for a better quality of life, I'd be happy to see that number be 30% or 35%. So there's nothing magic about proportion that's spent on drugs. And although it's getting a lot of attention because the number is high, what we really care about is value, which is the total cost of care necessary to get through a given endpoint.

So if you do something that changes an endpoint that either gets you to a better outcome or provides cost offsets, that's a good thing. So again, it may be that and likely will be that with the oncoming inspector of all the new therapies, which we're excited about, that, that number will go up and should go up. I worry more about some of the high-cost drugs and for things like toenail fungus, where we don't see the value.

I think -- so I think this is a good agreement and important one. And as you heard before, the likelihood is that with additional screening, which Alnylam and others are promoting that we'll see more cases of hereditary ATTR amyloidosis, which makes these kind of agreements even more important. But I think this also is relevant and newsworthy because I think it sends a message to other manufacturers that even when you've got this -- a condition, which is complicated to measure, where it's not just an easy outcome measure and would require some effort to collect the data, that's not something we would see off a claim, for example, or off of a lab slip, that even when those things exist, I think these are important. And in fact, I think these are going to turn out to be more important than some of the lower level type of agreements. And I think showing leadership in that area is something that should get attention. And I hope that others follow.

So those are my formal comments. I'll -- happy to take questions now or later, however Alnylam wants to go forward here.

QUESTIONS AND ANSWERS

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

That's great. Thank you, Dr. Sherman. Maybe one question that's come up. You mentioned about 15 VBAs. You've already entered in 2. Anything you've learned? What's worked well or what's been a particular challenge in trying to implement those various VBAs?

Michael Scott Sherman - *Harvard Pilgrim Health Care Inc. - Chief Medical Officer and SVP*

Yes. Well, a couple of things. First, there's got to be enough juice to be worth the squeeze. And there've been several where companies have done them to, I think, to put out a press release. If it's only -- and again, as I said before, there are proof of concepts, that if you do something which is a couple of percentage points, yes, you can show that it works and settle up. But those aren't going to persist because they, frankly, are not material. I think we've also shown and are starting to show that even in cases where it's hard to collect the data, that may be where it's worth the most worth doing. And my point is that, yes, it's easier to -- and more scalable for collecting something based on diabetic results or hospitalization. But if you're talking about a rare disease, where the difference between success and failure may be a couple hundred thousand dollars for that patient, it makes perfect sense for a payer to think creatively and hire a staff person to collect that if they need to. I'd also add with EHR connectivity and health plan setting access, this is getting easier and easier. And I think the most important big picture point here is that when I first started pushing on this a couple of years ago -- I meant 3, 3.5 years ago, and pharma companies would say, "No, we can't do this. We don't know how to head the next question." And so to those who said, "Oh, we can't. Here's all the reasons why we can't." I think the fact that we've been successful shows, yes, we can. And we've seen either more pharma companies joining. We've seen more payers and PBMs joining. So I think we've particularly -- maybe the most important point is we validated the model that this is a viable tool in our armamentarium to attack the issue of balancing access and affordability. And then, I guess, finally, I'd say that one other learning is this is not the answer. So it's interesting because I've been at the forefront of this. So I

find myself on what goes, as you might imagine, on more than a few panel discussions. And what surprised me is about a year ago, when I finally afforded and found myself on discussions, where they were talking about what's likely to be the percentage of value-based agreements in 3 or 5 years, and they were actually the most pessimistic. And what I realized is that the consultants and other provocative thought leaders on the panel have really never done this. And they were saying, "Oh, it's going to be 50% or 70%." When I look at, again, where the juice is worth the squeeze, where there are clear measures, clear cause-and-effect partnership opportunities, the right time, of course, all of the things that matter, I actually think it should be reserved for a certain subset of drugs, which I mentioned before. So one of the learnings is, no, the entire world will not be value-based agreements in 5 years.

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

That's very interesting actually. One other question that came in if you could answer. How much does Harvard Pilgrim Health Care spend on prescription drugs annually?

Michael Scott Sherman - *Harvard Pilgrim Health Care Inc. - Chief Medical Officer and SVP*

We spend -- well, again, when we talk about our drug spend, we -- prescription drugs, I would -- so I count both pharmacy benefit and the medical benefit that are administered in the physician office. But I would say, and I'm not giving you the exact number, but I would say it's north of $0.5 billion. And we're a midsized plan with 1.3 million members. So it's in the hundreds of millions of dollars, north of $0.5 billion.

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

Okay. Thank you. And maybe your thoughts on, as you mentioned, Harvard Pilgrim Health Care is more of a midsized player. Do you think VBAs are more likely to be helpful as a midsized or a larger or a smaller? Or do you think it doesn't matter on scale of the insurance company?

Michael Scott Sherman - *Harvard Pilgrim Health Care Inc. - Chief Medical Officer and SVP*

That's a good question. Let me answer a related question first, which is why I think we're one of the leads in this. And there's various reasons, and I won't try to answer that comprehensively. But -- and part of it has to do just with our thought process, where I think the opportunities are, et cetera. But with respect to size, I think we're in a sweet spot. And if you think about it, we're big enough that we have resources and we have great analytics and a great pharmacy department. And we don't outsource every function to PBMs, for example. And in fact, we're one of the few that actually does their own rebate contracting. So we'd have both the skill set, the mindset and the mechanism. And if we were smaller, I'm not sure we'd have that kind of scale or that kind of expertise. On the other hand, if you're bigger, and without talking a lot about my background, I worked previously before this at Humana for a couple of years, and before that at UnitedHealthcare. And one of the things about organizations like those, and I remember trying to do some innovative work and have some success around some alternate payment models that were provider-based. But it seemed like there was always someone who could stop you, who wasn't bought in, who might have a different agenda or maybe just was busy, too busy to meet with you and understand and work collaboratively, but could create barriers, whether it's people in the network area or legal or product or whatever. So we're also -- so while we're big enough that we have resources, we're small enough and occupy a point in the organization where I can pretty much easily say we're doing this work -- if there are a couple of stakeholders that are concerned, speak with them about it and work through them. So for getting these done, I think we're in a sweet spot. Now the related question though is, where do they have value? I think they have value everywhere. But -- where you see the first steps are going to differ. But once they're validated, and you see that there's a benefit, I would expect everyone to join on. Again, for the large ones, the larger health plans, they certainly have the capabilities. And if they see it as a successful model, you get less pushback and less internal obstacles. And then through the smaller ones, I think we will see more of that either through -- facilitated through intermediaries like PBMs, where we're seeing other intermediaries that are sometimes hired by the pharma companies, third parties like Truven or Real Endpoints or others that are collecting data and helping adjudicate the plans, et cetera. And I think those help some of the smaller players. So these are beneficial, but it should be beneficial to any payer that's in game.

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

Excellent. Well, thank you very much for those questions. I think at this point, we'll now switch over to Rena to talk about ATTRsc02, and we may have more questions for you, Dr. Sherman, at the end also. Rena?

PRESENTATION

Rena Denoncourt

Thank you, Eric, and hello, everyone. My name is Rena Denoncourt, and I am the Program Leader for Alnylam's ALN-TTRsc02 program and ATTR amyloidosis. Alnylam has been and continues to be deeply committed to bringing innovation to patients of ATTR amyloidosis. Today, I'm pleased to provide an update on the development status of our investigational RNAi therapeutic, ALN-TTRsc02.

As you may know, we have completed the Phase I clinical development and healthy volunteers. Today, I will briefly recap the clinical study data from that pre-clinical study. Also, earlier this year, ALN-TTRsc02 was granted orphan drug designation in both the United States and Europe for the treatment of transthyretin-mediated amyloidosis. This designation covers both hereditary and wild-type disease. Also over the past year, we have been proactively engaging with regulatory agencies, key opinion leaders and payers to establish a clinical development plan that will address the heterogeneous need of the broader patient population.

Outlined on the right side of the slide, you can see a subset of the potential product attributes of ALN-TTRsc02. These include potent and sustained TTR knockdown. The potency of this module is anticipated to result in a duration of action that will enable infrequent quarterly dosing and require only a small volume of drug, which can be subcutaneously administered. Additionally, since a fixed dose will be required for injection, we expect to develop ALN-TTRsc02 in a pre-filled syringe presentation, which will enable simple self-administration at home. We expect to initiate our pivotal Phase III study named HELIOS A in hATTR amyloidosis patients in late 2018. Today, I will provide details on the upcoming HELIOS A Phase III study design as well.

Here you can see the ALN-TTRsc02 Phase I study. It included 80 healthy volunteers. As you can see from the study design, cohorts were screened, and then randomized 6:2 to receive a single dose of ALN-TTRsc02 or placebo. The graph shows that ALN-TTRsc02 achieved robust and durable serum TTR knockdown. The TTR knockdown was potent and sustained in the manner that supports further evaluation of a quarterly dosing paradigm. A mean max TTR knockdown after a single 25 mg dose was approximately 83%. As such, this 25 mg dose level has been selected for an upcoming Phase III pivotal study. Importantly, in this Phase I study, there were no serious adverse events 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% TTR knockdown level with ALN-TTRsc02 after repeated quarterly dosing.

Our next step in the clinical development program is for ALN-TTRsc02 is the HELIOS-A Phase III pivotal study. We have reached alignment with the FDA regarding the study design that I'll walk you through today. The study will include a co-primary endpoint, including mNIS+7 and Norfolk Quality of Life. This open-label study will include a primary efficacy assessment at 9 months, and that assessment will be a comparison of the ALN-TTRsc02 arm versus the placebo arm of the APOLLO study, which as you will recall was the pivotal study for ONPATTRO, which went out last year. Additionally, The HELIOS A study itself will include a small reference comparator arm of patisiran-dosed patients. Beyond this study, additional Phase III studies, including a study in patients with wild-type ATTR amyloidosis, are under discussion and planned for 2019.

Now I will walk through the HELIOS A study detail, though still preliminary. Importantly, the inclusion/exclusion criteria of the study will be very similar to those of the APOLLO study to enable a robust comparison across the 2 studies. Patients will have a confirmed genetic mutation and a Neuropathy Impairment Score, or NIS, between 5 and 130, just like APOLLO. Also mirroring APOLLO, prior tetramer stabilizer use followed by a washout period and will be permitted for patients enrolling in HELIOS-A, the study will include a randomization, which will result in approximately 120 patients receiving ALN-TTRsc02 dose once every 3 months at 25 mg and approximately 30 patients receiving patisiran dosed once every 3 weeks at 0.3 milligrams per kilogram. All patients will undergo a thorough efficacy assessment at month 9. A similar efficacy assessment will take place at month 18, and patients will participate in a treatment extension portion of the study thereafter.

Again, the co-primary endpoint will be the change from baseline on both mNIS+7 and Norfolk Quality of Life. Secondary endpoint will support a comprehensive assessment of disease burden. These will include the 10-meter walk test, modified body mass index and an assessment of the patient's ability to conduct activities of daily living via a questionnaire called the Rasch Overall Disability Scale, or R-ODS. Additionally, at the 9-month time point, TTR reduction in ALN-TTRsc02-dosed patients compared to the patisiran-dosed patients will be assessed.

Given the findings from the post-hoc 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 certain cardiac measures, such as NT-proBNP and echo parameters as well.

In summary, I'd like a touch upon 4 key design elements that are important to keep in mind about 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 and ethnicities are represented within the study population. Additionally, the study design includes similar inclusion and exclusion criteria to that of the APOLLO study. This will enable cross-study comparison between ALN-TTRsc02 arm on the HELIOS A study and the placebo arm from the APOLLO study. The design is useful as it will leverage the rigorously studied data set from the placebo arm of APOLLO, for which we have patient-level data to enable a robust comparison. The design also has the benefit of supporting a smaller patient population than may otherwise have been required in a pivotal study, which will support faster completion of the study. Our inclusion/exclusion criteria will, again, result in a study population that will include multi-systemic disease manifestations and a range of disease severity.

Another parallel to APOLLO that will be leveraged in the HELIOS-A study design will be the comprehensive clinical evaluation at baseline 9 months and beyond. Many of the same well-established tools that we use in APOLLO for thorough evaluation of disease burden in hATTR amyloidosis patients will again be applied to the HELIOS-A study to assess the change in neurological impairment, quality of life, ability to conduct activities of daily living and cardiac manifestations of disease. And finally, similar to patisiran, ALN-TTRsc02 will harness RNAi technology. Utilizing the natural and catalytic mechanism of RNAi with this highly potent molecule, the study will evaluate a 25-mg dose administered subcutaneously once every 3 months with anticipated similar reduction in serum TTR levels to that seen with patisiran and APOLLO.

That pretty much wraps it up for the study design. So I look forward to bringing you continued updates on the progress of the HELIOS-A study over the coming years.

And with that, I will turn it back to Eric.

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

Thank you, Rena. So please remember to submit your questions now for any of the speakers. As we await for a few more questions to come in, let me briefly summarize.

2018 has already been a transformative and historic year for both Alnylam and for our TTR programs. Receiving the first ever approval of an RNAi therapeutic in both the U.S. and in Europe in August was immensely gratifying and marks a new stage of Alnylam's growth as a global integrated research and development and commercialization company. We are actively launching in the U.S. and gearing up in our initial launch countries in Europe, plus preparing for further regulatory filings in Japan, Canada and Switzerland yet this year. And with ALN-TTRsc02, we continue our commitment to ATTR amyloidosis patients by developing a therapeutic option that we expect to enter into late-stage development later this year. And as you can see from the table below, we have already achieved many of our objectives this year with several more expected to be completed in the next few months.

So with that, I will now move on to some questions. And as a reminder, please submit any of your questions you may have by Ask A Question button located in the slide window above the webcast player.

QUESTIONS AND ANSWERS

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

I have one question that I will ask of Rena to start. So you just walked through the details that we preliminary believe for HELIOS-A, but I don't see any mention of wild-type patients despite the orphan drug designation that spans the entire disease. What's the plans for adjusting those patients?

Rena Denoncourt

Yes. So the wild type population will be the topic of another study. It will not -- wild-type patients will not be enrolled in HELIOS-A. However, it is definitely part of our longer-term development plan, and our study in the wild-type population is under active discussion for -- starting in 2019. We're going to develop that study design and engage with regulators to ensure that it meets their expectations, and then the expectation will be to move forward with that in 2019.

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

And previously, it's been mentioned, I think, publicly the potential for that study, that second study you just mentioned to be against tafamidis. Any thoughts on that?

Rena Denoncourt

That is one design that we're actively including in the discussion. It would certainly be an option that is requiring further consideration, and is of interest to assess the feasibility and the interest with our key opinion leaders and patients regarding a head-to-head design that could include tafamidis.

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

Excellent. Thank you. Another question back on HELIOS-A. Any discussions with the FDA? Have they mentioned wanting to see an active control arm in the study?

Rena Denoncourt

We have looked at what it would take for an active control arm, and it would require a very large study. So we have also the beneficial position of having the body of data from APOLLO with that patient level data, and really a contemporaneously assessed placebo arm that would be a suitable comparator in the eyes of regulators. So that's the approach that we've decided to take.

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

Very good. Another question on here, HELIOS-A doesn't have just mNIS+7 as a primary endpoint like APOLLO, it actually has the 2 co-primary endpoints. Any color on that?

Rena Denoncourt

Yes. So you'll recall that the Norfolk Quality of Life was the key secondary in APOLLO, as you reviewed earlier, Eric. And based on the feedback from the FDA, actually, we did decide to elevate the Norfolk as part of the co-primary with mNIS+7 and Norfolk together. It really does serve to provide the benefit of showing the impact of how the patient feels on therapy. And there's certainly worth including it in as a co-primary endpoint from our perspective. So we agreed to the FDA on that perspective.

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

Excellent. I think switching to a question for Dr. Sherman. With VBAs now being discussed more, are you hearing any demand come from your clients, basically, the companies? Are they asking for more of these VBAs in any way?

Michael Scott Sherman - *Harvard Pilgrim Health Care Inc. - Chief Medical Officer and SVP*

I don't know that I would frame it that way. The answer is not really. What they're -- but what they're asking for us is -- what they're saying is they're concerned about rising drug costs, and they want to know what we're doing about it, and particularly what we're doing about it that is different than just saying no to drugs that their employees require. So VBAs are kind of the answer. I don't think that your average employer knows enough to demand VBAs, for example. I'd also note that it's interesting. These things go in cycles. I think all the HR leads, that employers, I guess, belong to the same organizations, go to the same meetings. A couple of years ago, it was travel medicine, medical tourism. Then it was telemedicine. Recently, it's concierge services. But they're also all starting to ask us proactively about the drug cost, even saying, "Come in. Tell us what our top 10 drugs are and what you're doing about it." And that never happened before. So they're demanding that we do something, and they're leaving it to the health plans to see what they can do to help them manage their expense.

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

Thank you. Next question, it looks like it popped up, which I don't now if we have the answer for you. The question really is probably about the key to the second study we talked about in the cardiac involvement were you aiming to enroll? What New York Heart Association class would you be included? I think we're probably too early in our design discussions for that.

Rena Denoncourt

So for the HELIOS-A, if the question is about the HELIOS-A study, the heart involvement, the cardiac involvement parameters will mirror the APOLLO study parameters. To that extent, they will not include NHYA Class III in that HELIOS-A study. However, in the future, more cardiac-focused studies that we will do in 2019, we have not finalized the cardiac parameters for those studies.

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

Excellent. Thank you. And back to Dr. Sherman, another question. How much more quickly is a Harvard Pilgrim member potentially able to access ONPATTRO because of a VBA?

Michael Scott Sherman - *Harvard Pilgrim Health Care Inc. - Chief Medical Officer and SVP*

I don't really know the answer to that because I don't know what our competitors are doing. What I can say is that any -- when we do a VBA, this is also something we've done with others in the high-cost innovative space. There are agreements and reviews that are taking place before the drug is approved before the PDUFA date, not afterwards. Now in theory, that could take 3 to 6 months after that to come up with a policy. So one could argue that you're accelerating -- because I can't say compared to competitors, but I can say compared to our not having agreement, we would probably need another 3 to 6 months to finalizing our policy. In the interim, of course, even when it's not covered under "new to market," we were always going to review things on an ad hoc basis. But formally speaking, it's probably 3 to 6 months.

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

Related to that is a question probably for us, Alnylam. Regarding innovative contracting, how does the payback or rebate option align with CMS' best pricing guidance? We believe you stated publicly that our value-based agreements that we would enter into would be capped at the limit

that would not trigger best pricing. So that's the important part for us to protect on how large of a rebate to go and any possible impacts on government to pay.

Michael Scott Sherman - *Harvard Pilgrim Health Care Inc. - Chief Medical Officer and SVP*

I'm sorry. If I can also add a perspective. So yes, as a player, one of the constraints we face is Medicaid best pricing. And I certainly can understand why pharma companies would not want to risk crossing that line, again, for reasons that were very obvious. But I also think that as we see more high-priced drugs, particularly one-time therapies like gene therapies, et cetera, we're going to have to figure out how to pay over time commensurate with success and involvement. So there's a lot of questions happening, both on The Hill and at CMS and HHS offices. And I know that because I've been a part of them to try to solve it through either legislative means or waivers. That said, it's complicated, and there's no easy fix here.

Rena Denoncourt

Right.

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

That is, definitely. It looks like a follow-up question from earlier. Rena talked about how to address the wild type. We think we may address the wild-type population. But a question, the hereditary patients that have predominant cardiomyopathy, what's the thought there?

Rena Denoncourt

Certainly. The vision for the ALN-TTRsc02 program is to be able to address throughout the broad comprehensive population with ATTR amyloidosis. So certainly, the HELIOS-A study will include patients with hATTR that will have a level of polyneuropathy that mirrors the level of polyneuropathy expecting -- or that was present in APOLLO. But additionally, the future of the clinical development plan absolutely does envision including patients that have both wild-type ATTR as well as the hereditary ATTR with predominant cardiac manifestations. It's under discussion. We have not solidified exactly what our approach will be. But certainly, we will not leave those patients behind, and we will work to make sure that we address the broad ATTR population in a comprehensive manner.

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

Okay. And then a question that's come up is, assuming positive success throughout the study of the TTRsc02, what happens to patisiran or ONPATTRO when sc02 is approved?

Rena Denoncourt

Well, that is a good question. But certainly, for patients, it is our belief that, that choice is really good. What we want to be able to ensure is that physicians and patients can have a meaningful discussion at the individual patient level to find the right treatment option that meets the individual needs of those patients. So basically, both products will -- assuming positive new drug clinical development of ALN-TTRsc02, both products would potentially be available, and the patient and the physicians can use as they see fit at the individual patient level.

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

And there are other examples of other disease areas where an infused product does maintain a significant portion of the market share. I believe that ONPATTRO in some patients and some physicians that will be served will be doing well. Their disease will be managed that they feel it's appropriate and may choose to stay on ONPATTRO. We've actually had some patients talk to us and say that they actually enjoy going to the

infusion center, gives them a chance and reason to get out of the house. It gives them an ability to interact with other patients. So I think that will be a very interesting world in a couple of years to evaluate. So I think that brings another question about over a view of the home infusion option for ONPATTRO, and we have talked about here in the U.S. specifically that home infusion is available now as an option as -- for some patients after evaluation and recommendation by their treating physician, but it may not be covered by all insurance plans. So this is an example where Alnylam Assist can be beneficial to patients to help them understand what options they have for receiving ONPATTRO. We have generated some experience with home infusions to our global OE programs, so those patients that completed APOLLO, and have rolled on to the open-label extension studies. So we do have some data, mostly in Europe, on home infusion also. Another question here, are -- in the U.S., are our reps able to call on cardiologists? And what can they discuss when they go there? The answer is yes. Given the multi-systemic nature of hereditary ATTR amyloidosis, the large number of definitely specialists' call points that may see these patients makes it very appropriate for us to go and educate on the disease and help these patients get to a diagnosis sooner and, hopefully, the accurate diagnosis. These include, obviously, the neuromuscular specialists, neurologists, including cardiologists and also gastroenterologists. Let me see if any other questions have come up. So any concerns with enrollment on HELIOS-A, given that ONPATTRO is now on the market?

Rena Denoncourt

The availability of ONPATTRO does vary throughout the world at this point. We have approval in the U.S. and Europe, but it is not yet available in all European countries. And then, certainly, the HELIOS-A footprint will be broader than even in Europe. So as we -- early in the study, we will be in countries where the commercial availability of ONPATTRO would will not yet be concurrently available for patients. In general, again, this will be -- it could be a decision at the patient and physician level about if they wanted to participate in a clinical study or if they wanted to go on commercial therapy. And that would be something that will be left in the hands of the patient and the physician, given the unique needs of that patient.

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

Thank you. Dr. Sherman, another question back to you. There's a little bit of confusion sometimes when people think about VBAs. Will patients get their money back under a value-based agreement, as we've discussed here?

Michael Scott Sherman - *Harvard Pilgrim Health Care Inc. - Chief Medical Officer and SVP*

Yes, that's a good question, and the answer is probably not. And the reason for that -- and although that could change, and the reason for that is as follows. And when we look at the cost share borne by the member as opposed to by the payer, it's got getting smaller and smaller. And over the past 5 or 6 years, we've looked at it, it's rough from $0.35 of the dollar to $0.20 in 2017. Meaning out of every dollar that is paid for drugs, and again, we're including medical benefit all-in and pharmacy benefit, $0.80 of it is paid by the payer and $0.20 by the member. Now I don't know what the right number is, but it is a balance because, again, to the extent it's paid by the payer, that means if you recall my -- one of my intro comments, that's paid by everyone that goes into premium. So there's kind of a sweet spot there. Now if you think about therapies that cost hundreds of thousands of dollars, again, for -- we're weighted to the way benefit designs are set up, and the fact that there are limits under the ACA, et cetera. Generally, the individual is paying no more than a few thousand dollars of that under our plan designs. So if we get back a certain amount of money that if not successful, it would seem, at the margin, virtually all of the dollars were paid by the health plan. So using -- putting that money back into the plan or putting it another way using it to offset premiums for everyone would seem to make more sense, given where the dollars came from. There are exceptions to that. For example, our agreement with Amgen, where there's a 100% refund under certain circumstances, obviously, would lead to the individual getting back their out-of-pocket as well. The -- what makes it a little messy is that there's various legislations to -- and efforts to provide rebates in general back to members. And so it's unclear what that legislation might do to basically force us to return them.

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

Excellent. Thank you, Dr. Sherman. And another question for you then, it looks like. Any cap on the VBA? Will that be similar to Spark's turnout 23.1%? This may be related to the question we answered a little bit earlier also.

Michael Scott Sherman - *Harvard Pilgrim Health Care Inc. - Chief Medical Officer and SVP*

Again, anything -- I never talk numbers with the press generally. We keep that confidential. But obviously, Alnylam can share whatever it would like to.

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

Good answer. And for our final question given the time. Given the recent ATTR-ACT data, are you concerned about initial ONPATTRO uptake in the first few years? We've said previously that overall hATTR amyloidosis is very underdiagnosed or even misdiagnosed. So commercial success will be closely tied to medical education and patient funding efforts. Thus, if we assume tafamidis is approved for wild-type ATTR amyloidosis in the U.S., then Pfizer's added disease awareness efforts to increase diagnosis of the disease can only really help the overall market opportunity. We believe that the ONPATTRO data shows improvement across a broad range of severities and mutations. And given where we're labeled in the U.S. and even a slightly broader label in the EU that includes cardiac data, we believe we will be quite competitive if and when tafamidis is approved.

I think with that, we are a little bit out of time. So I want to again thank Dr. Sherman for his time and Rena, both for sharing their insights and perspectives. And I'll turn it over to Christine.

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

Great. Thanks, Eric, and thank you to the rest of our speakers as well. So this concludes our RNAi Roundtable for today, and also marks the end of this year's RNAi Roundtable series. The replay and slides of this roundtable will be posted on the Capella section of the Alnylam website later today at alnylam.com/capella, with the transcript to follow shortly thereafter. Replays and slides from all of our roundtables in the 2018 series can also be found on the Capella section of the website. Thank you, everyone. Have a great day, and goodbye.

Rena Denoncourt

Thank you.

Michael Scott Sherman - *Harvard Pilgrim Health Care Inc. - Chief Medical Officer and SVP*

Goodbye.