Operator^ Thank you, ladies and gentlemen, for joining today's RNAi Roundtable. We will be conducting two web based question-and-answer sessions during the webcast. You may submit a question at any time during today's presentation by clicking the Ask a Question button located above the slide window on the webcast player.

I would now turn the call over to Ms. Cynthia Clayton for opening remarks. Cynthia, you may proceed.

Cynthia Clayton^ Good afternoon, everyone, and thank you for joining us for today's RNAi Roundtable to discuss the progress we are making with our program and development for the treatment for Hypercholesterolemia.

I'm Cynthia Clayton, Vice President of Investor Relations and Corporate Communications for Alnylam. With me today Akshay Vaishnaw, our Chief Medical Officer; Dr. Christie Ballantyne of Baylor College of Medicine; Kevin Fitzgerald, Alnylam Senior Director of Research and the Program Lead on our PCSK9 program; and David Kallend, VP and Global Medical Director at The Medicines Company, our partner for this program.

I will be turning it over to Akshay shortly who will provide you with a brief introduction, but first a few comments. Today's will end at about 5 p.m. Eastern Time. We will be taking questions from you via the webcast and you can submit a question by clicking the Ask a Question button on the webcast player. Akshay will moderate a Q&A session with Dr. Ballantyne and then with Kevin and David at the conclusion of their presentation.

As a reminder, we will be making forward-looking statements and we encourage you to read our most recent SEC filings. And with that, I will turn it over to Akshay.

Akshay Vaishnaw^ Good afternoon, everybody. At Alnylam, we have been proceeding with our 5x15 strategy effectively over the last few years. Just a reminder to those of you
that are not familiar with this, it's a reproducible and modular part for genetic medicines. Why do I say that, because with RNAi we could use siRNA's to target any gene in the genome and specifically with the delivery advances we've made over the last few years we have been targeting a variety of genes in the liver.

Using this approach, we can go for genes addressing high unmet need diseases and validated by human genetics. Most recently our success with the GalNac conjugates has allowed us to develop subcutaneous approaches with a very wide therapeutic index. The 5x15 strategy which starts with validated genetic -- with genetic targets picks up then with proof of concept in Phase 1 where these targets are associated with blood-based biomarkers.

For example for those of you that have been following our work over the last few years, you've seen our proof of concept data in transthyretin amyloidosis or in hemophilia where we've shown using RNAi based approach, knocked down of the relevant genes with a reduction in circulating TTR or thrombin, for example.

And with proof of concept in Phase 1, we can rapidly advance to a definable path to late development and here we utilize established endpoints in a range of diseases with a focused to pivotal trial and looking forward to significant treatment effect. We've been doing this work collaboratively with a host of constituencies including physicians, regulators, patient groups, and payers.

Turning to the next slide using our reproducible and modular approach with RNAi, you can see we've created a very significant pipeline of opportunities. There's almost a dozen different targets and indications listed on this chart. They fall into three broad areas, genetic medicines which address the series of orphan disorders such as TTR amyloidosis and hemophilia and targets and indication addressing the cardiovascular metabolic space of which is PCSK9 is an example. And finally, most recently we've expanded our interest into the infectious disease arena with a program in the Hepatitis B space.

I want to now highlight the subject of discussion today which are -- which is our program against PCSK9 our program which we termed ALN-PCSsc.

This drug addresses different forms of Hypercholesterolemia as we'll discuss shortly, the clinical trial application is on target for late in 2014 and we intend to have initial Phase 1 data by the middle of 2015.

So, with that brief introduction, I want to now turn the call over to Dr. Ballantyne, who will give us a very thorough overview of the Hypercholesterolemia space. Dr. Ballantyne?

Christie Ballantyne^ Thank you very much. So, if you can go to the next slide, these shows a pyramid, the title is “High-Risk for CHD Events Due to Extreme Elevations of Atherogenic Lipoproteins.” And so with the pyramid here basically at the top would be the people with the highest levels of LDL. And remember we measure LDL cholesterol
but they're really lipoproteins, you can measure ApoB or non-HDL, there's different ways of trying to quantitate the concentration of these atherogenic particles.

Homozygous FH should be at the top of the pyramid then heterozygous and it goes by the -- the base gets broader because we have more common disorders, familial combined hyperlipidemia. Elevations of (inaudible) and then the most common will be polygenic hypercholesterolemia.

So, let's go -- start off with the -- one, that's the most famous, familial hypercholesterolemia. And Brown/Goldstein got the Nobel Prize for this, they got that right around the time that the first statin came out and it was really important in terms of understanding -- here were people who had a mutation in the LDL receptor including the gene that clears LDL, if you're a heterozygous, you have one normal copy, one abnormal copy, your LDL's are twice normal and you begin to have heart attacks in your 30s for men and 40s and 50s for women. It's a fairly common cause of premature heart attack.

What's really striking is the unfortunate child who has two parents each who carry one copy and if they're unlucky they have the one in four chance to get two bad copies, now you have fewer -- functioning LDL receptors, six-fold increase in LDL and heart attacks in childhood and the famous story of when I was a resident at Southwestern, of a young girl who ended up with a heart and liver transplant, the heart transplant because she already had at age 6 multiple heart attacks and the liver transplant was a form of gene therapy to give her normal LDL receptors.

So, there's been some recent focus on homozygous FH, if you go to the next slide here, because it's an orphan drug indication with it. The frequency is about one in a million although in some areas it can be more frequent. There are other disorders besides just, next slide, mutations in the LDL receptor.

There's mutations in the protein that binds ApoB. PCSK9 gain a function, mutations cause high LDL, [a similar] phenotype. There’s an autosomal (inaudible) hypercholesterolemia and there's also phytosterolemia where there's excessive absorption. This is a slightly different pathway and therapy for that would be ezetimibe.

So, let's go to the next slide. Why so much focus on LDL cholesterol or lipoproteins that are related to LDL? So, this is because the genetics are extraordinarily consistent. Now, as shown on this slide here, you see this is the associations with LDL cholesterol of genetic polymorphism with multiple genes and you see PCSK9 for it once and several other genes and what ends up happening is that this shows the size of the impact on LDL.

The next slide shows the association with coronary heart disease, so all of these genes which have a significant influence on LDL also have an impact on coronary heart disease.

And the next slide shows that the impact is related to the change in LDL, so this is the concept of (inaudible) the randomization, nature has already done the experiment but the
genes had increased or lower LDL cholesterol impact coronary heart disease. It's very consistent.

So, the next slide talks about if we look at development of lipid lowering therapies, cholesterol, the first one was niacin in the '50s then you had the bile-acid [binding] resins. Endo found the first statin, and it was not -- it was an empiric method and you had fibrates, so it was really the last century took a long time and they were just really a few drugs that were developed and then we had a ezetimibe which also was found actually somewhat empirically, it wasn't really understood, there was blocking [NPC]-101 for it.

So, what -- that's a slow process, there weren't many drugs, there are a lot of failures if you look at this and why was it so difficult in this area? A lot of it ends up as how did people approach this, there was identifying the targets, it used epidemiology, there were animal studies and there was a very long gap between target selection and proof of concept studies in humans.

So, what's changing here is in this century by using human genetics, you can identify rare, uncommon variants which sort of are rolling key biological pathway. And as already mentioned, biotechnology is on several fronts can rapidly reduce the time for targeted identification of therapeutic trials.

The other thing that comes up in terms of targeted identification is now you've gone from just epidemiology to epidemiology plus the concept of many of the randomization to see, is your target in the causal pathway and that is a very, very important issue in regards to showing, I think, really validation that this might be beneficial for diseases like coronary heart disease or other diseases.

So, are there examples of this? There are some disorders with low levels of LDL cholesterol that have been known for a while whether these are rare disorders, apolipoproteinemia is mutation in the microsomal triglyceride transfer protein; familial hypo-beta is a mutation in ApoB that we've known that disorders was bile acid malabsorption cause low cholesterol, and also PCSK9, loss of function mutations cause low levels of LDL cholesterol.

So, if we go to the next slide and we look at new therapies, actually all of those genetic disorders that are related to low LDLs are in the pathways of the new therapy called (inaudible) was one of them; lomitapide basically is an MTP inhibitor; Mipomersen, an anti-synthesis to ApoB.

And then which is not out yet but which has gone at an extraordinary pace are the monoclonal antibodies to PCSK9 and which if you look at the time from the first description of the gain and function mutation, then the loss of function mutation and we already have Phase 3 outcomes trials with thee agents that are there in progress and it's been a very, very -- there's never been a program this fast in terms of identification to moving to Phase 3 in my knowledge and certainly in the field of lipid atherosclerosis.
So, go to the next slide. So if we look at epidemiology, you have the LDL data that's very strong but so is the HDL data. And here is where the generics helps is -- and it's funny, when I was a resident at Southwestern, Joe Goldstein is my attending -- I gave a lecture on HDL and he came up afterwards and he said, "Christie," he said, "I've looked at this since like 1985," and he said -- he said, just let me -- let me warn you, he said, "HDL is really complicated, the genetics are not straightforward, the metabolism is very complex," he says, "You don't really want to go that direction."

So he was pretty prophetic, HDL is a very complex in terms of genetics, most of the variants are associated with the HDL levels but not with coronary heart disease.

So, they failed this concept of [meeting] at randomization. If we go back to what Joe Goldstein had done in 1973 on the next slide for hyperlipidemia (inaudible) premature MI -- yes, high LDL's are common, but actually it was even more common to see people who had high triglycerides and high cholesterol, they're just high triglycerides.

So, there's been this signal for a long time about triglycerides and mixed dyslipidemias. And it was a disease, the next slide, familial combined hyperlipidemia, which is actually more common than familial hypercholesterolemia. FH is about 1 in a 500, this was about 1 in 100 and metabolically they have increased coronary heart disease, they make an excess number of atherogenic lipoproteins.

And the next slide turns out that this is actually not a single disease, there's lots of different genes that are related to this phenotype and it's very important to kind of in the modern era where we see this epidemic of obesity and diabetes where we have lots of people who have -- who have basically increased triglyceride lipoproteins, lots of small (inaudible) and they have increased risk for heart disease.

So, there -- this has been an exiting area also in terms of the field of lipoprotein atherosclerosis. Go to the next slide here.

If you look at these multiple genes, they've identified that alter levels of LDL cholesterol, triglycerides or HDL cholesterol, this [didn't] work, it's primarily even lead by (inaudible) that basically the beta coefficient for LDL cholesterol is strong as you predict but when you adjust for the different other lipid fractions for genetically determined variables, triglycerides hang in there and HDL drops south.

Now, in the epidemiological studies, it was the other way around. But if we look at these studies triglycerides seem to be important and if you -- genes that impact triglyceride levels, have a risk for CHD, the next slide, a recent New England Journal of Medicine paper, I'm the director of the Atherosclerosis Core Laboratory which is one of the trials that was involved of this ApoCIII loss of function carriers, one of the epidemiological studies.

But these are so -- if you look at rare genetic variants who had loss of function in the gene for ApoCIII, they have very low triglycerides compared to the non-carriers, there's a
reduction of about 50%. And on the next slide is that they have a -- overall about a 40% reduction in coronary heart disease.

Next slide. And what's -- the next slide says -- it should say gain of LDL function, gain of APOA5 function, allows ApoCIII function, reduces risk from MI. So, it turns out there's pathways that have been known in regards to the metabolism of triglyceride receptor proteins been involved -- we've known that C3 is involved, APOA5 and also ANGPTL3 and there's been increasing evidence of the importance of these genes in regards to not just lipoprotein metabolism but also coronary heart disease.

So, where do we stand in terms of -- which kind of -- which kind of individuals should get more intensive LDL lowering therapy? Well, in the 80s it was high cholesterol, then 90s we talked about measuring LDL cholesterol looking at global risk, 2,000 high-dose statins.

And I would say right now is that the next step will -- they'll be on -- is that you'll say, okay, I know, I want a another person who's at high risk after being treated with the statin or maximally tolerated statin. But their risk is high not because they're 99-years-old, their risk is high because they still have an excess of atherogenic lipoproteins. Then it's -- so that's a concept we know that basically if your LDL goes up, your risk goes up.

So the next slide here says, residual risk versus risk related to atherogenic lipoproteins. People may have a high risk for cardiovascular events. They're not driven by LDL. And we've seen this. If you have low ejection fraction and congestive heart failure that basically you're going to die through a process involving the myocardium and arrhythmias, it's really not a lipoprotein atherosclerosis driven process, same for renal [dialysis].

And there are groups that don't appear to have some of the benefit that others might have. So this is a slide out of a DYSIS study. The next slide, the [site spreading] therapy, many high risk patients have marked LDL elevations. And it was showing that -- this was in Europe recent study that basically a lot of people with heart disease after an advanced -- still have LDLS over 100. But even more importantly, it's the group that’s -- it's going to -- take it again, there should be group in red, that's on the far right where it says, 4 millimoles, that's around 160 milligrams per [deciliter] of LDL.

So there's still a sizable number of people who have quite high levels of LDL cholesterol with known heart disease. And that's true not just in Europe, but in the United States there's a number of such individuals with it.

So why does this happen still? Well, a lot of it has to do with the issue of statin discontinuation and intolerance. This was a study of a couple years ago but it's very common that people stop their statins. And sometimes they're not rechallenged. If you rechallenge them, you can usually get them to take a statin. But it may not be very high dose of statin.
And the new guidelines which came out and talked about people should be on high dose statins, this has been looked at in several databases; and it's a funny thing we see those are evidence-based guidelines, well there's evidence from clinical trials that if you get to - - take a high dose of statin, you'll have fewer events, but the evidence of clinical practice says that this doesn't happen anywhere in the world.

This is from many, many databases that you're looking at it in general around 15% to 35% of acute coronary heart disease are actually taking a high dose of a high efficacy statin. And there's a lot of reasons why there's push back or other things but they've been out for years and years.

And if Pfizer couldn't get people to use atorvastatin 80 milligrams with all the data they had, I don't think changing the guidelines is going to make that much of a difference with it.

So in conclusion, there's a spectrum of challenging patients. There are those with a rare monogenic disorders with extremely high levels of LDL and ApoB to those with much more common disorders. And I would point out that most of the people who have an LDL cholesterol that's over 190 or 200, don't have a single gene disorder, they have polygenic hypercholesterolemia.

But if you have heart disease and you've got polygenic hypercholesterolemia, it's just as bad as if it's -- that was from a single gene. And there was also a slew of people who have problems with triglyceride-rich lipoproteins that we really don't know what to do with.

The benefits of LDL lowering therapy are related to both the absolute level of LDL and the risk of heart disease in the individual patient and particularly is the -- what is the concentration, I think, of atherogenic lipoproteins.

And on maximally tolerated statin therapy, next slide on conclusions; many individuals continue to have an increased risk of CVD events due to atherogenic lipoproteins. And there is various reasons for this resistance of therapy; some monogenic disorders, some people because they have high Lp(a) and also intolerance to high-dose statins.

So in conclusion, where do we stand in this century compared to last century, we're a lot of better at identifying targets and that's a dramatically increased because of really the cost of sequencing. So like in the area cohort of 16,000 people, we're going to probably have the entire cohort having [excellent] sequencing soon. And I think full genome not too much after that. And that's along with all these individual disease of it. It's a vast amount of data.

And then speed of drug development. And you've heard already about the platform approach they can buy this company because they're able to really once the target's identified, there are approaches where you can rapidly come up with the treatment and then move out that to humans.
And with that, I will stop and open up if there's any questions about some of the things that I covered.

Akshay Vaishnaw^ That was great, Dr. Ballantyne, thank you so much. I think we do have some questions for you actually. And I -- here's one, I mean, it commonly comes up, you're an expert, you're a practicing physician. What proportion of patients can you get to target in terms of the LDL cholesterol using current approaches and I presume statin being the corner stone?

Christie Ballantyne^ Well, so first you have the question of really what is the optimal LDL? So we don't know the answer to that. In the US, they kind of gone away from targets. We used to say a target of less than 70. The European guideline stick to that and the data suggests that less than 70 are certainly better than that from many different studies.

In my practice, the referral practice of people who have problems. And so most of the people who come to see me, it's because they can't. And I can only see a small fraction of the people that -- or seeing like this.

But there are a very substantial number of individuals who on their -- and I think the way to look at this is the highest dose of tolerated statin are unable to reach what we would considered to be an LDL target level. And it's fairly common that this does not happen in practice.

Akshay Vaishnaw^ And so what proportion would be that be roughly in your hands do you think?

Christie Ballantyne^ So in my hands as I said, it's biased because the people sent to me are people who have problems with statins. Yes.

Akshay Vaishnaw^ Yes.

Christie Ballantyne^ But so and I -- but there's basically if you look into country, there's millions of people who are unable to get their numbers to where they should be who are at high risk, who have actually vascular disease or a risk status that would put them in the high risk zone.

Akshay Vaishnaw^ Right. You know, the most recent guidelines around control of LDL cholesterol level and the -- what do you think that's going to do to identification of patients and prescription of LDL lowering therapy?

Christie Ballantyne^ Well, I think the good thing is that they are -- they've changed the concept of what's risk and they've gone to a 7.5% being a high risk and over 5% being moderate risk where you might consider therapy. And they expanded that to include not
only MI and (inaudible) but also stroke. So that's actually going to be more people who would be considered for therapy.

There's some controversies with equations. But I think overall, it was in the right direction. Because what was done in the past was only to use an MI. So if you're from a patient perspective, if I have a heart attack, yes, that's a bad thing, but having a stroke is also a bad thing which is more common in women than men. And they still don't include having re-vascularization, a [standard] bypass in this equation.

So it's still truly an underestimation of someone's likelihood of having something bad happen. And I think we'll come to more and more and better ways of assessing global risk for individuals.

Akshay Vaishnaw^ Yes. One last question Dr. Ballantyne, then we should let you go. But what do see is the role for parental lipid lowering therapies? How well do you think they'll be adopted both the PCSK9 product we're talking about today, and in the future products targeting things like ApoCIII or ANGPTL3?

Christie Ballantyne^ It's been interesting when it's -- I was rather dubious of what the acceptance would be. But there really hasn't, I mean, we've been involved with lots of studies and people don't mind the injections. It's a twice a month, once a month and I think it will end up depending upon the side effect profile of the agent that's injected. And a lot of it has to do with their first experience with Mipomersen was a little bit tainted because you had this [flu] like syndrome.

And the injection site reactions were sometimes rather striking. So that has not been seen at least from your reports with your approach and also with the monoclonals. So the compliance has not been a problem in the monoclonal studies. And I think, diabetes, people do injections every day.

Akshay Vaishnaw^ Yes. No, you're absolutely right. And this is ultimately a life threatening disorder. Dr. Ballantyne, we have to thank you again for your input today and the excellent presentation. So thank you. We’ll let you sign off.

And with that, I think we can transition to Kevin Fitzgerald from Alnylam; and David Kallend, who will sequentially give us a presentation on the Alnylam ALN-PCSsc program.

Kevin Fitzgerald^ Sure. Thank you, Akshay. First, I just want to again to thank Dr. Ballantyne for a fantastic introduction. And in particular, the point about how in the modern day of developing medicines we're using really state-of-the-art genetics. And that's exactly what we do here. We've chosen targets that are very well genetically validated in humans.

In particular he mentioned a couple that are also in our pipeline ApoCIII and ANGPTL3. But the focus today what we'll be talking about is PCSK9.
As he mentioned PCSK9 is one of the best validated targets for lowering of LDL cholesterol. And the way that PCSK9 functions is to control the level of the LDL receptor or the receptor that clears bad cholesterol from the blood.

So in the excess of PCSK9, with a high PCSK9 level, you have a low LDL receptor and therefore you have very high plasma LDL cholesterol levels. If you inhibit a PCSK9 either by [sapping] up the excess that's in the blood through a monoclonal antibody approach or through the approach that we'll talk about today, which is actually to block the production or synthesis of PCSK9 to begin with, what you'll find is that you lower plasma LDL cholesterol significantly.

We've developed an initial RNAi therapeutics targeting PCSK9 that was formulated in a lipid nanoparticle. This was an IV formulation that we took into a Phase 1 clinical trial that was recently published in "The Lancet" in 2013. What we were able to do in this trial is to show proof of concept definitively that RNAi mechanism could work in man to lower PCSK9 as well as the clinically validated endpoint of LDL cholesterol.

So what this was, was a random placebo controlled trial. This was an IV -- single IV infusion where we were able to show up to 84% lowering of plasma PCSK9 with a mean lowering of 68% as well as major reductions in LDL cholesterol up to 50%.

So what about PCSK9 baseline values? And I'll talk about that throughout the talk. But baseline values do matter. Not everyone has the same PCSK9 level at baseline. In particular patients or individuals that are on statin have a very high baseline PCSK9 value because it's well-known that statins can up regulate the production of PCSK9 through the up regulation of the transcript.

And moreover, there've been recent studies such as the study presented here which is (inaudible) that are suggestive that high levels of PCSK9 in particular on patients on statins are predictive of cardiovascular events.

In addition, in the Phase 1 trial what we did is to look and indeed we had actually patients that started with different baseline values of PCSK9. These were relatively healthy subjects with elevated LDL cholesterol but they had different baseline values.

And what we were able to show is that by an RNAi mechanism which is catalytic, different acting than the antibodies and it's actually inhibiting the transcriptional up regulation by cleaving the transcript.

And it was able to lower LDL cholesterol equivalently independent of the baseline levels of PCSK9 in the serum.

And we'll talk -- we'll come back to that sort of as a theme later on. On the next slide; what we've done is to go back and manufacture a -- to develop a subcutaneous version of the drug that's delivered by an entirely new platform. And that is our GalNAc platform.
This is a simple platform where you've got a double stranded RNAi that's hooked to a ligand. And that ligand binds specifically to a receptor that's expressed at high levels in hepatocytes in the liver. So this is a liver directed delivery of a double stranded SI.

There are two types of chemistries that we'll talk about today. There's an initial chemistry which was the first stage of the platform which was called our Standard chemistry where we have gone into clinic in our TTR subcutaneous program.

And then I'll talk about an enhanced stabilization chemistry that has enabled us to increase the duration of effect and the potency of these molecules. ALN-PCSsc that I'll talk about is actually using the enhanced stabilization chemistry.

As you can see on the next slide, we had taken the original platform in our TTRsc program into a Phase 1 study to show human proof of concept for this platform in general. And what you can see on this slide is that ALN-TTRsc was able to significantly lower a serum TTR via subcutaneous injection up to 94% with a main knockdown of up to 92.4%.

The construct was -- the drug was generally well tolerated with the only AEs associated were mild injection reactions that resolved within approximately two hours of onset.

One thing to note on the right-hand side is we always like to try and predict from our pre-clinical models such as non-human primates, the duration of effect or the effects that we'll see in humans.

What we have noticed with this platform and in recently reported data for AT3 even more significantly with our enhanced stabilization chemistry is that we're getting greater potency as well as greater duration of -- in humans than we have seen in non-human primates.

So when we come to the PCSK9 non-human primate data, we're anticipating that we will see the effects will be longer in duration as well as that lower doses in humans.

So what you can see on the next slide is that; this is a non-human primate, this our initial experiment where we've looked at 2 milligrams per kilogram subcutaneously dosed; once daily for five days. And then we've gone with the three doses of the weekly maintenance. And what we have here is up to 95% PCSK9 plasma knockdown as well as up to 67% LDL cholesterol [knockdown]. This experiment is done in the absence of statins.

And what you can see we have stopped dosing at about day 25 with this experiment. And what you can see is a very extended duration of effect where we have a nadir effect of 67% that really stays flat all the way out to about day 90. So that's -- and we'll continue on this theme in the next couple of slides.

So in the next slide; what you can see is this is now a single dose response curve from 1 milligram to 10 milligrams single dose. And what you can see on the left-hand side is
that after a single dose of PCSK9 up to 10 milligrams per kilogram, we got up to 96% PCSK9 knockdown and up to a 77% LDL cholesterol going again in the absence of statins.

Now this is a very highly durable effect and we think that this will certainly support once monthly dosing or possibly once quarterly. You can see on the left-hand side that the knockdown of PCSK9 at 10 milligrams per kilogram goes out and is very flat through a day 100 similar to LDL which is quite flat-out to day 90.

Our initial safe -- pre-clinical safety studies have shown that we have wide therapeutic index. So we've done initial safety studies with this molecule [Q] weekly times five doses at 30, 100, or 300 milligrams per kilogram across three species that being mouse, rat and non-human primate. We have an NOAEL of greater than 30 milligrams per kilogram in all species tested. We have [NOAEL] findings; no significant changes in serum chemistry, ALT, cytokines, no injection site reactions, and no adverse histopathological findings.

We are planning a Phase 1 study with this particular drug. And the patient population initially will be a single ascending dose and healthy subjects with elevated LDL cholesterol. We'll then follow with the multi ascending dose, again, in healthy subjects and patients that are on or off a dose of statins.

The study size will be approximately 120 individuals altogether. And the treatment regimen for the multi ascending dose will be a Q monthly regimen to begin. Our endpoints will be typical and safety, pharmacokinetics, also we'll be measuring clinical activity as measured by the percent reduction of LDL cholesterol and PCSK9 compared to baseline and the duration of these effects.

Other measurements will be up HDL cholesterol, triglycerides, total cholesterol, ApoB, ApoA1, and Lp(a). We're planning a CTA filing late this year with initial clinical results expected in mid-2015.

So in summary, PCSK9 SC represents a novel approach for anti-PCSK9 therapy. It's a synthesis inhibitor and initial human proof of concept studies with ALN-PCS were able to show an up to 84% knockdown of PCS and 50% in LDL. ALN-PCSsc uses our enhanced stability chemistry. It shows us very potent and durable PCSK9 knockdown as well as LDL cholesterol lowering in non-human primates and our single dose data support Q monthly, or possibly Q quarterly subcutaneous dosing regimen.

We expect that the human translation of this platform has been validated in clinic with ALN-TTRsc as well as ALN-AT3 and our new ESC chemistry improves potency and duration. We have a wide therapeutic index with an NOAEL today of greater than 300 milligrams per kilogram. And again, we expect to file in late 2014 with the initial clinical results expected in mid-2015.
So what about the potential differentiation versus anti-PCSK9 monoclonal antibodies? There are two points that I want to talk about. One is clamped PCSK9 knockdown as well as LDL cholesterol lowering with monthly or, possibly, quarterly SubQ dosing. And that this level and this effect is independent of whether you have a very high baseline PCSK9 value or whether -- and will also be a low subcutaneous injection volumes anticipated to be less than 1 mil.

Also via this mechanism which access the transcript level -- not at the protein level, we do anticipate that there's potential that we could synergy with statins. And I'll talk about these in the next couple of slides.

So the next slide is a figure taken from Blom et al. this year of 2014. And what this is showing initially is that individuals do have different baseline PCSK9 values as you can point out here going left to right. They're individuals that were on diet alone or diet plus two different doses of statins or two doses of statins plus ezetimibe.

And as you go from left to right, it's pretty clear to see that the patients that are on high doses of atorvastatin and ezetimibe have the highest baseline PCSK9 values because it's been up regulated by those treatments. You can notice that the highest dose 420 milligrams, this particular antibody is able to have strong initial binding to PCSK9 as measured by the percent change in free PCSK9 protein.

And what you can see on the next slide is that, however, four weeks post-dose, if you then again look at the levels of PCSK9 in particular those levels of individuals that are on to statins those baseline values are coming significantly up higher.

And the percent change in free PCSK9 is now less than 50% and it goes -- and it's less as you go from left to right as the baseline values increase. And that's likely simply a result that they have higher baseline PCSK9 values and therefore the antibody which is binding stoichiometrically to the protein is not doing quite as well.

To highlight that again, this is an earlier study quoted and it's a figure taken from McKenney et. al. and [JACC] in 2012. And what you can see here is again, at a monthly dosing regimen and I've chosen the 200 milligrams per kilogram, I wanted to highlight in blue that what you see in a monthly dosing schedule with this antibody is that you do get a recovery of LDL cholesterol between doses. And so there's a bit of a saw tooth pattern in between doses when you dose this monthly.

If you contrast that on the next slide to what we're seeing with a monthly dosing regimen, I've shown here in non-human primates, this is a study where we've dosed 6 milligrams per kilogram as a loading dose. And now we're coming back with 3 milligrams per kilogram once monthly. And you can see a very flat pattern of LDL cholesterol as well as PCSK9.

This data again, we've seen up to 90% PCSK9 knockdown, 77% LDL cholesterol lowering. It's in the absence of statins in these animals. The data minimally support Q
monthly. The study is still ongoing. And we're looking to extend this out to a quarterly dose in regimen.

In addition, as I've mentioned before with our ESC chemistry, we've seen in our program in clinic for AT3, I can refer you to that roundtable that we expect to see significantly lower doses be effective in humans than you see in non-human primates. And that's about an approximate tenfold. So based on human translation, we expect to be less than 1 milligram per kilogram and less than 1 milligram with this drug.

On the next slide, just to highlight initially base on the knockout mouse data where a genetic knockout of PCSK9 was shown to be at least additive and potentially synergistic in its activity with the statin. But the trial results to date suggest a lack of anti-PCSK9 monoclonal antibody synergy with statins.

And again, we believe that we may differentiate based on our mechanism of action which is acting at the transcript level and has that -- we have a catalytic activity, so one siRNA can actually down regulate or degrade a large amount of messenger RNA whether it's upregulated or not. And so we believe that we have a chance at seeing minimum -- at minimum, an additive effect of a potential synergy with statins.

So, with that, I think I'll turn it over to David Kallend to take us through the Alnylam Medicines Company global alliance. David?

David Kallend: Thank you very much, Kevin. Good afternoon, everybody. At The Medicines Company, we're very excited to have the opportunity to be involved not only in [interesting] new class of treating for LDL cholesterol but also to collaborate with Alnylam in this development. As you've heard, there's some very exciting science forming the basis of this therapy and so far some very promising data [that] Kevin and his team have done.

In terms of a collaboration to advance the program, we're looking to create an industry leading effort for best in class medicine where possible for PCSK9 antagonism. In terms of the deal structure, there's a $25 million upfront payment and then a series of milestone payment up to a total of $180 million. And after that, should we be successful [in] scale, double digit royalties on global product sales.

In terms of the actual clinical development program, Alnylam will complete a certain preclinical and a Phase 1 study. At that point The Medicines Company will take over the lead and development of Phase 2 to commercialization but also the strong collaboration throughout the course of this program, we have joint meetings on a regular basis.

If we move to the next slide, this shows us what we believe is to be a successful collaboration. As you're all aware The Medicines Company is globally established in the acute cardiovascular care arena, we’re very familiar to cardiologists and with the collaboration with Alnylam, the ALN-PCSsc subcutaneous, we’re able to expand the cardiovascular portfolio into a more chronic therapy for these cardiovascular patients.
And in terms of [The Medicines] team that will be working on this program, very experienced team, many of us with more than 15 years of experience in the cardiovascular area both in hypertension, heart failure and also lipid developments. And as I'm sure you're all aware, we're currently developing MDCO-216 which is ApoA-1 Milano for short term therapy in ACS patients, so that we have the experience and a good collaboration to move this development forward.

QUESTIONS & ANSWERS

Akshay Vaishnaw^ Good. Well, thank you for that and I think Kevin and David gave us an excellent overview of the program and the collaboration. Let's go to questions now and see what we've got.

Here's one, David maybe you want to pickup on this. Amgen and Regeneron, Sanofi are much further ahead in clinical development with the antibodies. Do -- does Alnylam or Medicines Company have any particular concerns about not being first to market with the PCSK9 inhibitor? What do you say, David?

David Kallend^ Yes, that's a very good question, I think it often comes up. I think there are several aspects to this, both positive and negative. I think it's always nice to be the first in the class, I think that this treatment, at this point, we won't be given the advance stage of the other competitors in this class.

And I think that sometimes coming at a later entrant may also have some advantages, having worked in the statin area for many years and doing one of the latest statin to the market, we just (inaudible). I think you learn from others in the class, you learn what’s required in terms of the clinical trials, you learn for the regulatory environment and I think that's also would be some advantage, you learn from the clinical trials done by the competitors.

I think in terms of the patient population, this is the large population, there's a lot new patients coming along and it teaches like the statin market and it tends to be the new prescription that are -- is where there's a change in the business. So you look at -- [much] switching, you probably won't get much switching in these class, it's all about having a profile that's competitive and able to get a significant share of new prescriptions once you're on the market. So it's already down to the profile.

At the time you launch the (inaudible) potentially best in class, but there's obviously a long way to go at this point.

Akshay Vaishnaw^ Indeed. And so you're pointing to the example of later entrants statins like atorvastatin, which went on to take the leader position, yes

So, if we turn to the clinical trials space, here's a question. Why is Alnylam going back to normal healthy volunteers, why don't we go straight into patients with the Phase 1 effort? Maybe I can take that.
In fact, we'll be incorporating both healthy volunteers and patients in the Phase 1 study and the goal would be to rapidly get through the ascending doses of the study with healthy volunteers to establish the safety.

And then as we get to the interesting dose levels, we'll, of course, also be studying patients who have abnormal LDL levels on and off statins and I think we'll be able to defensively show in that context that we have an exciting therapeutic on our hands.

So, next question. I think, Kevin, you've had interest in this area, are there small molecule inhibitors of PCSK9 and what's known about them or how do they perform?

Kevin Fitzgerald^ To date, I really don't -- I know of no small molecule inhibitor that's gone into clinic for PCSK9.

Akshay Vaishnaw^ Yes. Yes.

David Kallend^ Now, just to add to that. There are -- there are three, I believe, three small molecules in the discovery phase and how -- the mode of action is unclear but there are certainly reputed to be small molecules drug (inaudible) PCSK9.

Akshay Vaishnaw^ Okay. Kevin, there’s interest in going over the preclinical profile, you commented on a wide therapeutic index based on the preliminary toxicology study. So what types of tox studies have been done with species and what's the NOAEL and what are the findings?

Kevin Fitzgerald^ Yes. So as I mentioned in the talk, we have done preliminary talk studies in mice, rat, as well as non-human primates and to date, the NOAEL is 300 milligrams per kilogram or greater, that being the top dose that we've tested and that was once weekly for weeks, we're in the midst of a GLP talks campaign that's dosing once every other week.

Akshay Vaishnaw^ Very good. Okay. This is a question that's been posted but often comes up, and that is how do Alnylam and The Medicines Company feel about the RNAi approach to PCSK9 inhibition as compared to the monoclonal antibody approach? And I suspect you both might want to comment on that. Kevin, RNAi versus antibodies?

Kevin Fitzgerald^ Yes, so as we -- as I had stated before, we had a section on where we believe we will be able to differentiate to sort of cap that. I think we're going to clamp PCSK9 down, we are a different mechanism that is a catalytic mechanism that works at the RNA level, so we believe that will be effective no matter what the baseline levels of PCSK9 are.

And particular in patients that have very high PCSK9 levels. And again, because of that PCSK9 is cleared through the LDL receptor, those patients tend to be individuals that
have partially defective or defective LDL receptors who actually are on statins. So it's a very high risk population.

We believe that will have potentially a best in class duration of action, so our dosing frequency, we believe will be best in class and we believe by mechanism that we could potentially be synergistic with statins.

Akshay Vaishnaw: Good. David, do you want to comment on the RNAi approach versus the antibody approach to PCSK9?

David Kallend: Yes, I think just to add what Kevin said, obviously, there’s all the scientific angle and everything. I think at the end of the day, it's down to patient benefit and which of the therapies allow patients have the greatest reduction in cardiovascular risk and that remains to be seen, of course, and there's also the aspect of how easy it is for the patient to take the meds, and it is going to be a small volume, it’s going to be less frequent. So (inaudible) at the end of day, it’s can we provide a solution which improves patient outcome in this population.

Akshay Vaishnaw: It’s funny you said patient -- you know, injection volume compliance and so forth, there's a question on that. What do we expect to be the typical dose level roughly and the injection volume and the frequency of injection and how will that improve compliance? Kevin, have you got anything on that?

Kevin Fitzgerald: Yes, so given our experiences with this platform in AT3 and again, I can refer you to the AT3 roundtable, but we anticipate that the dose levels will be approximately tenfold less than what we've seen in non-human primates and that the duration could be significantly longer. So we're looking at less than 1 mil volume, you know, certainly once monthly, potentially once quarterly, or longer.

Akshay Vaishnaw: And that would probably lead to an improvement in compliance as well, I suspect.

Kevin Fitzgerald: Yes.

Akshay Vaishnaw: Yes. Good. The question is reason about CNS or neurocognitive adverse events about some things have been said about in association with the antibodies and, I believe, the FDA has asked for additional testing to be done in association with the antibody based programs. The question to ask is, have we observed any neurocognitive adverse events in the previous phase 1 study with ALN-PCS02. Kevin?

Kevin Fitzgerald: So, we did not. And one thing I will point out about the program is to date, we've actually -- we've seen absolutely no exposure of this particular platform in the brain.

Akshay Vaishnaw: Good. And has the FDA requested that you make an assessment of these types of events in the program?
To date, they have not.

Yes. Okay. Let's now turn to PCSK9 levels. And Kevin and David, do you want to comment on the question here, why do you emphasize levels of PCSK9 and how that could influence the outcome [us] versus the antibodies. Kevin?

So the data is coming in, and there’s been other data out there that have been published that high PCSK9 levels are not good things to have. In particular, you know, in addition, you know, with high PCSK9 levels, if an antibody is binding stoichiometrically, you'll need more drug on board, it makes sense to bind those high levels.

In addition, statins upregulate PCSK9 at the transcript level, which is exactly where our mechanism is working and has a very wide dynamic range. So we believe that our -- our opinion or our particular drug will behave independent of PCSK9 levels, and that having lower PCSK9 levels has been proven better through human genetics.

Yes, good. Just last couple of question because we're going to run out of time soon, but David, maybe you want to take this. What do you expect if we were to combine ALN-PCSsc, someone has written if it was to be combined with a statin?

Well, I think we expect to see shortly [send it all] -- the drugs in this class are probably an additive effect and since the LDL, say, reduction, I think we have to remember that statins will always remain the baseline therapy for these patients, unless the patients are unable to tolerate the statin. So we expect to see an independent effect, an additive effect on top of statins that it’s potentially going to lead to patient benefits. So I don’t think it's going to be a good combination for the patients that require (inaudible) cholesterol alone.

Kevin, anything to add to that?

Yes, I think you know, I definitely agree with Dave. I think there's also a chance when the data will come in when it comes in our phase 1 trial or maybe in phase 2 that we see a synergistic effect based on mechanism.

I think we've got time for one more question, and the question is, today on the call regarding the -- we're going to have a preliminary data for the ALN-PCSsc program in phase 1 interim data in the middle of next year or so, what data are we expecting and what will we share? Maybe I can address that.

First and foremost, it’s the first in human studies, so safety will be important and we hope to demonstrate excellent safety just as we have done with our other conjugates to date, which will include ALN-TTRsc for the TTR amyloidosis program and the AT3 program for hemophilia. So safety will be important.
In addition, pharmacokinetics data will be presented and then finally, and probably of highest interest will be pharmacodynamic data. And during Kevin's talk, you saw the range of endpoints we’ll be measuring in association with this very important new lipid lowering drug and chief among them will be data referring to LDL cholesterol.

So I think it will be a very exciting time to find out just how well the monkey data translates into man, and if the TTRsc data are anything to go by, I think we anticipate some very good news indeed. So more to come in the middle of 2015.

I think it's time to wrap up, is it Cynthia?

Cynthia Clayton Yes. Thanks very much. This concludes our RNAi Roundtable for today. The replay, slides and transcript will be posted on the Capella section of our website later today.

We hope you've been enjoying our RNAi Roundtable series and look forward to your participation next week for our two final roundtables. On Wednesday, we will discuss the ALN-AAT program for the treatment of Alpha-1 Antitrypsin Deficiency-Associated Liver Disease. And on Thursday, our ALN-AS1 program for the treatment of Hepatic Porphyrias. Thanks very much, everybody, and have a great afternoon.