Alnylam Pharmaceuticals
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Corporate Speakers

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- Laurence Reid;Alnylam Pharmaceuticals;SVP and Chief Business Officer
- Rachel Meyers;Alnylam Pharmaceuticals, VP - Research in RNAi Lead Development

PRESENTATION

Operator: Thank you, ladies and gentlemen for joining today's RNAi Roundtable. We will be conducting a web-based question on the session during the webcast.

(Operator Instructions)

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

Joshua Brodsky: Good morning, everyone and thank you for joining us for our RNAi Roundtable to Discuss the Advances and Delivery of RNAi Therapeutics with Enhanced Stabilization Chemistry or ESC -- GalNAc-siRNA Conjugate.

I'm Josh Brodsky, Manager of Investor Relations and Corporate Communications at Alnylam. With me today are Laurence Reid, Senior Vice President and Chief Business Officer at Alnylam and Rachel Meyers, Vice President of Research in RNAi Lead Development at Alnylam.

In moment, I'll be turning it over to Laurence who will provide you with the brief introduction, but first just a few comments. Our RNAi roundtable today focuses on ESC GalNAc-siRNA conjugate is the second in a series of roundtables that we are hosting over the summer weeks to review recent progress we have made with RNAi therapeutics. Today's event will end at about 12.00 p.m. Eastern time.

We will be taking questions from you via the webcast and you can submit questions at any time during the event by clicking the Ask-a-Question button located above the slide window on the webcast player. Laurence will moderate the Q&A session with Rachel at the conclusion of her presentation.

As a reminder, we will be making forward-looking statements and we encourage you to read our most recent SEC filings for a more complete discussion of risk factors. And with that, I would turn it over to Laurence.

Laurence Reid: Thank you, Joshua. Good morning, everybody. This is Laurence Reid at Alnylam. I'm very pleased to introduce our second roundtable on our GalNAc technology platform.

On slide 6, I just want to really put the technological discussion that we're about to embark on into the context of our Alnylam's 5x15 product strategy. What we've really demonstrated we believe now over the last -- I think over the last 2 years or so of the clinical another data that we've shared with you is a technology of RNAi -- Alnylam RNAi technology platform really has created an ability for Alnylam to move down a very reproducible and modular path by which we're able to generate and advance our genetic medicines and that path has 3 fundamental components one of which we're going to really drill into in detail this morning.

The first component number 1 on the left-hand side of the slide is really a capability now to modulate any gene expressed in the human liver essentially at will. We then focused, of course, on target genes that are validating known to be involved in disease that has both a high unmet need and where the target has been -- has reached a very high scientific standard of validation ideally to human genetic demonstration.

Deployment then of our GalNAc-siRNA platform enables us to administer these drug candidates to human beings subcutaneously and we've demonstrated now that we have a very wide therapeutic index in all the animal and human analysis that have been performed to date. So, that's the fundamental technical approach that we're taking to developing drug candidates against human targets.

As we look forward from there, Phase II of the second phase if you will of this part is to really look to achieve proof of concept very early in clinical development. So, we are looking for blood-based -- blood-based biomarkers that have a strong disease correlation and you'll see numerous examples of this as Rachel presents data to you this morning, but some of the best examples that you have heard us talked about include serum levels of TTR demonstrating knockdown of that protein in TTR of amyloidosis patients, modulation of thrombin generation in our hemophilia program, LDL levels and in our [psck9] program, HBs-antigen levels will become the biomarker for our HBV program.

So, molecules that are able to be very easily measured in the blood of our volunteers and patients in our -- in our clinical studies, and so we get to prove a concept very early in clinical development. And then the third piece is really just to extrapolate from there through [latest] development onto the market seeking the work in indications where they're very clearly establish endpoints where we can run the focus trials in well-defined patient populations seeking demonstrable significant treatment effects of which are really linked back to the caliber of targets that we're able to select.

And then we're building a very broad commercial strategy based on that by being very interactive from [early] development right through when our products reach the market in years to come and that approach encompasses relationships with physicians, regulators, patient groups, and payers over time as we move towards the market.

Slide 7 is snapshot of our development pipeline at it stands today. The lead program, of course, patisiran was the subject's of last week roundtable, ALN-TTR02 as it was previously called that's an LNP, a lipid nanoparticle-based product, and as you are aware because that's in early Phase III. Next generation ALN-TTRsc product for development and also against TTR amyloidosis with a focus on the cardiomyopathic form of that disease is what's referred to now as a standard template chemistry GalNAc conjugate through the first generation of GalNAc and Rachel will review some of that for you.

The rest of the pipeline has now evolved really based on very significant advances that we've made around the chemistry of our platform to what we refer to now as enhanced stabilization chemistry which really the focus of what Rachel will discuss this morning. And so all the drug candidates that you see in the light blue color on the rest of the slide from our 5x15 programs including plus hypercholesterolemia program this is partnered with the Medicines Company, new HBV Program and some other [blood] disease programs and other aspects of dyslipidemia, triglyceridemia all of those products now are using the ESC GalNAc conjugate platform.

Lastly, from my introduction here, on slide -- moving to slide 8, all of you are aware, building an IP portfolio to support the technology of products that we're building in Alnylam has really been a fundamental and very core piece of our corporate strategy since, you know, since day one of Alnylam and we have a very broad ranging set of intellectual property that covers our products, multiple product -- multiple patent families that some of which we talked about historically, some which are more recently under control by Alnylam really support and cover the GalNAc products that we're talking about today and both of our -- both the [nutritional] patents that have were licensed to our Alnylam really from day one of the company and other very important patents including the McSwiggen patent portfolio that we acquired when we acquired the siRNA RNAi acids from Merck at the beginning of this year each of those patent families cover the products we're talking about.

We also able to announce just recently the allowance of what we're referring to as the Manoharan 478 patent which provides additional protection on the products that Rachel is going to be describing. So, this patent claims that are -- had just been allowed cover a modified RNA agent linked any biantennary or triantennary ligand. So, it's a very broad set of claims includes all the GalNAc technology, the GalNAc conjugated RNAs that we'll discuss today but importantly it also covers single or double-stranded

molecules of any length and any sequence, and therefore, towards any disease target. So, very broad path, we're very excited about supporting our approach and particularly of siRNA approach into the world of GalNAc conjugates.

So, with that, I will hand it over to Rachel to really walk you through the state of the art of ESC conjugate technology. Rachel?

Rachel Meyers: Thank you, Laurence and good morning to everyone. So, I'm going to, as Laurence said, I'm going to take you through some of the advances that we've seen in the platform with the specific emphasis on subQ GalNAc conjugate strategy in particular, and to do so, I'm going to give you examples from a variety of our disease programs.

I'm going to share some data from our TTR Amyloidosis Program in which we have 2 drugs as Laurence mentioned, one called patisiran which is currently in Phase III and that's our LNP-formulated siRNA nd the second is called ALN-TTRsc which is currently in Phase II and that's our first inter [clinic] GalNAc conjugate siRNA for subQ delivery. I also share some data from our hemophilia and rare bleeding disorder program in which the target is antithrombin and the drug ALN-AT3 is currently in Phase I and we've got some exciting new data from that clinical program which I'll share with you [I know] at the end of this presentation. And finally, I'll share some data with your from our Hypercholesterolemia Program targeting PCSK9 and the drug ALN-PCSsc, again, is GalNAc conjugated siRNA for subQ delivery and that program is currently in preclinical study.

So, if you see on slide 11, that's really a simple representation of the challenge that we faced over the last 10 years and simply stated the challenge is, how do we convert a very large highly negatively charged extremely water soluble molecule into a drug that circulates through the body and transit across the cell membrane and that's what we've focused our attention on over the last 10 -- and then I will share with you those -- the advances that we've made. If you look at slide 12, you see another representation of this challenge which we've broken up into several [parts].

So, of course, we recognize that as we introduced one of our drugs into [susceptible] circulation. It needs to circulate and it needs to find the target tissue of interest which in the case of our Alnylam drug is the liver. After that it needs to access the specific cell type in the liver that is expressing the target of interest and in, again, in the case of our drug that is specifically the hepatocyte, and then further once it gets into the hepatocyte, it needs to actually get through the cell and enter into the cytosol where it can engage with the functional machine that's the RISC machine which does -- which performs RNA interferon.

Every one of our drug has to transit through this path to get to this protein machine called RISC and what I'm going to share with you over the next 30 minutes or so is some of the data that we collected that suggest of how we've handled and tackled these challenges to get access to this incredible intracellular machine, that is RISC.

And so what you can see on slide 15 is an overview of the two forms of the platform as Laurence already alluded to. The first form of our GalNAc conjugate strategy is called the STC conjugate which stands for standard template chemistry and that's the first form of the drug that we introduced into clinic in the form of ALN-TTRsc you can see on the left. We have made advances in that platform which we call our Enhanced Stabilization Chemistry platform or ESC platform and you can you see on the right and the first example of that, that headed to the clinic is our [AT3] program and importantly on this slide what I'm sure you recognize is that we've had a significant boost in potency as a consequence of moving from the STC conjugate to the ESC conjugate.

So, I'm going to start on the STC conjugate and really introduce you to the conjugate technology and then we'll move on to ESC after that. So, on slide 17, what you can see really the basis of the uptake in delivery mechanism that we're deploying across all of our drugs moving forward and that is schematically represented as an siRNA with a triantennary GalNAc illustrated here, and the function of that triantennary GalNAc is to very specifically and with a high binding affinity bind to a receptor on hepatocyte called the [A cell] glycoprotein receptor. That upon binding you get internalization into and endosome, you get a

trafficking through the cell, you get release of that siRNA into the cytosol where it can engage with RISC and you get nice recycling of that receptor back to the cell surface to get ready for another round of uptake and intercellular distribution.

We love this receptor and this receptor-ligand pair. This receptor is incredibly highly expressed on hepatocytes to the tune of about a million copies per cell. It recycles very rapidly; gets back to the cell surface in about 15 minutes and importantly, it can [serve] across species. So, what you'll see as we march through some of this data, you see experiments in mice and in rats and in non-human primates and in human, and we're always able to use the same drug and the same receptor ligand -- ligand pairing.

If you move to slide 18, what you'll see is a little bit more detail of the architecture of this ligand, and so you'll see on the top right-hand side some of the work that we've done to really tease out exactly what the spacers and the linkers need to be attached on siRNA and so you'll see the valency is all [straight] as triantennary, so we put three sugars onto this siRNA and we always link them through the same attachment point which is through the three prime end of the sense where the passengers strand of an siRNA.

On the bottom right which you'll notice, in the box you'll see the published binding affinity for ligand so they're either biantennary so that's the GalNAc2 or triantennary GalNAc3 and you'll see you get about a 10-fold boost in binding affinity to single-digit [nano molecule] when you go up to triantennary construct, and if you look at the graph just next to it, you'll see that when we actually take those ligand append them to an siRNA and evaluate that binding affinity in culture in primary hepatocytes, we see exactly the same binding affinity.

If you -- I want to point out to you if you look at the top figure for the GalNAc, you'll notice on [R] group there and that R group turns out to be extremely important as well for understanding the binding affinity and that we played around with that R group and there's lots of data in the literature to support that the exact structure of that sugar and the exact R group has a significant impact on binding affinity which I'll show you on the next slide.

So, if you look on slide 19, you'll see an uptake assay in primary hepatocytes and where we've tested several different ligand and several different competition strategies to really get at [the best specificity of this receptor ligand interaction. You'll notice that if we put a glucose instead of a galactose on that siRNA, we get no uptake. If we add a biantennary GalNAc onto the siRNA that's the third purple bar, we see some amount of finding but it's significantly enhanced in terms of uptake when we add that triantennary ligand onto our siRNA.

It's competeable by [EGCA] because it's is calcium-mediated binding interaction. It's competeable by the ligand itself, this triantennary ligand in solution and it certainly shows a significant decrease in activity when you eliminate the receptor, and all this data really support the idea that we're looking at a very specific receptor-mediated uptake mechanism for these siRNAs. Consistent with the very high expression of this receptor on hepatocytes if we do in vivo distribution experiment that subQ dosing in a rat, what you can see is that the vast, vast majority of the drug accumulates in the liver and there's very little drug in any other tissues that we've looked at with the exception of kidney which is the site of clearance of this drug.

When we've looked at Cmax level, we can see between 30% and 70% of the drug getting to this target tissue in the liver at a very early time point which I'll show you in a couple of minutes. So, we've taken this GalNAc targeting strategy and appended it to a siRNA and put this drug which is [ALN-TCRS] assay into clinic in a Phase I study in normal healthy volunteers, and on slide 21 which you can see is dose-dependent target down modulation getting to level of greater than 90% of decrease in TTR -- circulating TTR levels with a nice sustained effect and then a slow recovery back to baseline.

The dosing paradigm used here was a daily dosing with first five days followed by weekly -- 5 weekly doses after that and really importantly one of the -- one of the things that we learned -- consistently what we've learned from our [TTR02] or patisiran program is that if you look at the graph on the right, you see a very nice concordance between the data that we're seeing with respect to knockdown in non-human primate and in humans. And so if you look at timepoints per timepoints, dose per dose, during the dosing

period of the studies at a variety of doses you see very good correlation between non-human primate and humans and that suggested to us at this time that we could really use non-human primate as the way to evaluate how our drugs were going to behave in human.

OK, so with that really I'm going to take a turn now and introduce you to some of the advances that we've made in the platform as a consequence of introducing this Enhanced Stabilization Chemistry, and if you -- if you look at slide 23, that systematically represents how we thought about it. So, what's important to note here is that the GalNAc-targeting ligand is identical, the linkers and spacers that we put on the siRNA are identical. The site of attachment is identical, and in fact the sequence of the siRNA identical.

And what we've really found is that if we introduce different chemistries -- different positions on an siRNA, we can come up with a significantly improved compound and I'll start showing you some of those data on slide 24. So, if you look at the metabolic profiling map on the left-hand side of slide 24, what you can see is the difference between two compounds that are the same with respect to ligand, the same with respect to the sequence but they differ in the distribution of chemistries on the siRNA, and you can see in this by looking at the arrows, the size is cleavage in the liver, in this case, it's an 8-hour time frame which are reflective of the metabolism of this drug and the first thing, of course, that you noticed is that the ESC conjugate has significantly enhanced stability much less cleavage, much less metabolism.

The translation of that on the top right is in a very different AUC profile. So, if you look at the light blue from -- if you look at the light blue graph, you can see a very, very much broader AUC for this drug. So, we get much more drug to deliver and it's lasting for longer, it's quantitated on that table on the bottom and you can see a very significant increase in AUC. Not really much of an increase in Cmax.

On slide 25, we see the translation of that. So, what happens is a consequence of this extended metabolic stability and has extended a -- see and that really translates into an incredible increase in potency. If you compare in purple, Standard Template Chemistry and this is now a compound -- this is our AT3 [compound], the Standard Template Chemistry, you can see the single-dose 10 mg/kg. You get a modest 30% target knockdown if you take that, again, that same sequence with that same ligand and now you add this Enhanced Stabilization Chemistry, you can see a significant boost in potency greater than 10 fold and this is really what we expect from this platform across all of our targets.

As we started to probe this further in really trying to understand the PK/PD relationships on slide 26 we ask the question does the level of drug that we see at the target tissue correlate with the amount of knockdown that we're seeing, and not surprisingly, if you look on the left, if we ask the question for the total [amount] of drug in the liver, we see drug that accumulates at early times in the purple graph as our 4-hour [maximum] starts to clear but the peak of knockdown of our -- of our target in this case AT3 is at about 5 to 7 days through messenger RNA and is sustained and then recovers over time.

It doesn't correlate with the peak of drug in the tissue but in fact, if you look on the right what you see it correlates very well with as expected is the amount of drug that's captured in the RISC enzyme and so if you do an IP of RISC and you measure the siRNA that bound to RISC, what you can see is an absolute correlation between the peak of siRNA loaded into RISC and the peak of knockdown. You'll also notice, of course, that siRNA now has a very different kinetic profile and so it peak later and it's going to sustain the [duration] of a much broader AUC for drug and RISC as you would expect, so this enzyme-mediated reaction.

If we want to quantify that, on slide 27, and when we ask the question how much drug you actually need at the target site in order to get target knockdown what you can see on the left is you need about 100 nanogram per gram to get about 50% knockdown effect with expected total drug in the liver, and if you look on the right and ask how much drug you need loaded into RISC, amazingly you need only about 1.5 nanogram of siRNA per gram of tissue and that translates to just a few hundred molecules of siRNA that needs to be loaded into risk to get this ED safety effect and that really speaks to the incredible potency of this catalytic intracellular mechanism.

Of course, as I -- as I alluded to and as Laurence pointed out in the beginning, this platform is translatable across the number of targets. Here's the [SR] PCSK9 program in which we did an experiment in non-human primate introducing a single dose of siRNA at between 1 mg/kg and 10 mg/kg and you can see dose dependence, target modulation at 10 mg/kg. We focus on PCS you can see this -- you can see a sustained effect out to about 100 days and you can see, again, a consistent knockdown of [ol] cholesterol as you would expect when we modulated PCSK9 and what this really showed us for the first time was the incredible durability of this platform.

This data really suggested to us that although we had originally been looking at weekly dosing paradigm. We really are now set up with this platform to contemplate monthly or even potentially quarterly dosing and that's an amazing advantage (inaudible). It really opens up a lot of possible therapeutic opportunities that might not have been available to us initially.

We can understand that in addition -- in addition to being able to translate this across targets, we also know that this is really -- the GalNAc platform is really meant to be a multi-dose platform. If you look on slide 29, you can see the comparison in taking the same compound as a single dose in non-human primates. Again, this is from our AT3 program as compared a multi-dose, and if you just look at the ED80 line. You can see an ED80 at about 10 mg/kg in a single dose experiment. If you do that same experiment in multi-dose, in this case, weekly dosing, you can see an ED80 at about 0.5 mg/kg. So, we've had greater than a 10-fold increase in the potency of this drug when we converted to multi-dose and, of course, all of these GalNAc conjugates will be delivered as multi-doses.

On slide 30, what you can see is the beautiful sustained and consistent knockdown that we can see over very long periods of time. This is an experiment in mice using a mouse, rat specific Enhanced Stabilization Chemistry version of TTR compound and what you can see at either ED56, 60 doses or ED80 doses given weekly is very, very consistent and stable knockdown which in this experiment we get out to a greater than 9 months and then we ended the experiment and importantly we see no evidence of tachyphylaxis or sensitization and this is incredibly consistent and durable silencing and in fact no changes in the serum TTR level in our controls either. So, we have a very consistent and stable platform here.

If we move to slide 31, what you'll see is how we've applied that in our AT3 program with our drug which is ALN-AT3. On the left, you can see the beautiful potency of this molecule. So, if you follow the dark blue graph, you can see half mg/kg weekly dosing gets you down to 90% silencing in non-human primate. If we allow that to recover and it comes back in with lower dose of about 0.125 mg/kg, we can see we can reset the level of [thrombin] to about a 50% silencing effect at this incredibly low dose which is also stable, and this experiment really takes us all to that 6 months and showed the incredible durable stable silencing that we can give even in a non-human primate.

Importantly for the AT3 program, we're able to show in a -- induced hemophilia model in non-human primates that we could restore thrombin generation in this mild hemophilia by introducing the anti-thrombin drug. So, if you compare the first 2 pre-dose versus hemophilia, what we've done was we've induced hemophilia using an antibody, against Factor VIII in these [monkeys] and you can see evidence of the hemophilic state by decreasing thrombin generation in that [saline] group and we can restore that thrombin generation back to baseline levels by introducing our ALN-AT3 molecule and decreasing AT3 levels back to baseline.

And with this data and lots of other pre-clinical data that we generated in the AT3 program, we went into clinic, and on slide 32 is the summary of what we've seen so far in our Phase I study which is a two-part study in which the first part is a randomized single-blind, placebo-controlled single ascending dose study in health volunteers where we've [capped] the maximum allowable knockdown to 40% and then part B of the study, we moved on an open label multiple ascending dose study in severe -- in moderate to severe hemophilia patients.

Of course, the goals of this phase I study are safety and tolerability both in healthy volunteers and hemophilia patients, and importantly, we have the ability to look at some nice secondary endpoints which

include AT knockdown, as well as thrombin generation. And much to our surprise and pleasure, what we've observed in the study is that we actually had incredible potency.

So, we started the study at [event] what we -- what we perceived to be a very low dose of 0.03 mg/kg and what we've observed is about 30% knockdown of the target that we measured in circulation at that 0.03 mg/kg dose and consistent with that knockdown we saw a boost in thrombin generation. That's a result that is an improvement over what we saw on non-human primates and represents the real advance to this platform which [I'm going to] summarize for you on the next slide. Based on this 30% effect, we immediately moved into the multiple ascending dose, Part B of this study and we're currently now [on patients] and we look forward to reporting out on the preliminary results of that trial later in the year.

So, if we summarize data that I've shown you on slide 33, what you'll see is a table that tries to highlight some of those results we've seen from TTR and AT3. So, that top box shows you our ALN-TTRsc, our Standard Template Chemistry and these are data in humans which are consistent with the data we saw in non-human primates for TTR. In the middle box, you see our ALN-AT3 program and data from non-human primates, and in the bottom is this early data that we've gotten from a human studies of ALN-AT3.

And importantly what you can see is if you compare the box -- if you compare the data from TTR and AT3, we see a significant 5 to 10 times increase as we go from TTR to AT3 which is really going from our Standard Template Chemistry to our Enhanced Stabilization Chemistry. We see as I described to you a significant increase in potency about 10 fold when we go from single dose to multi-dose and that's evidenced in non-human primates in our AT3 program, and really beautifully, we can see additional increase in potency when we go from non-human primates to humans and that, again, is illustrated in our AT3 program.

I'll just point you to the fact that in non-human primate, a single dose, we had about a 25% knockdown effect at 0.3 mg/kg whereas we get this same level of knockdown at 0.03 mg/kg in human. And so all pooled if we compare where we started with TTRsc to where we are now with ALN-AT3, we see about a 50-fold increase in potency going from that earliest Standard Template Chemistry to where we are in humans with AT3.

How do we think about why we're seeing that improvement? Well, we're just starting to really understand that. On slide 34 is a little of a bit teaser about what we're thinking about and so what you'll see on the left is a metabolic profile of siRNA in comparing a liver S9 extracts from non-human primates and humans and what you can see is that there's significant difference in the metabolic profile where you see many fewer metabolites in humans suggesting that there is more stability of the siRNA in the human liver S9 extract.

Similarly, if we isolate cytosol attraction from mouse, non-human primate or human, what we can see, again, is a very significant difference in the amount of full-length proteins -- full-length siRNA that we see. Importantly, we see almost no full-length protein left at the 24-hour timepoints when we look at mouse or liver cytosol attraction and we see about 65% of the drug still remains, again, suggesting that in the context of human setting, our siRNAs appear to be more stable that is in non-human primates, there's a little bit more of an aggressive nucleus requirement and that increase stability appear to be translating to an increased potency and durability of effect.

I would be remiss, of course, if I didn't mention to you on slide 35, the beautiful safety profile that we have for these GalNAc conjugates. On the top, you can see the data that we have from our GLP studies with our ALN and TTRsc, that's our Standard Template Chemistry. And of course, we see no cytokine or complement activation and we've done studies in rats and non-human primates going up to 300 mg/kg in 5 daily dose paradigm followed by a 5 weekly dose paradigm for a total of doses, and importantly, in rats, we see modest findings in the liver which suggests a little bit of vacuolation in the liver and a very, very slight increase in LFTs and these are findings that were very, very consistent with what we've seen for all the nucleotides in the rat across many, many different programs and many different modalities of drug.

But really importantly in non-human primates, when we do that same dosing paradigm up to 200 mg/kg, we really see no adverse findings. It's clean -- it's -- no ISRs. We see no in-line findings, no clin path, no

histopath and we have an NOAEL of 300 mg/kg and that is based on everything that we know about all the nucleotides is really the non-human primate that's more predictive of what we're going to see in human. We're currently doing GLP chronic tox study which, again, are at the same doses, 6 months in rats and 9 months in non-human primates and we don't have the data yet but a quick look at the 6 month mark suggested things are -- that these drugs remain quite well tolerated.

We started to do some experiments, of course, with the ESC GalNAc conjugate and a similar story seems to be emerging no cytokine or complement activation and preliminary tox experiments in this case weekly dosing out to about 5 weeks so far doses up to 300 mg/kg are quite safe and well tolerated. We're still seeing anyway else of about 300 mg/kg, no ISRs, not really any in-life findings, no serum chem changes, and we anticipate, of course, as we continue the dose escalate is very likely that we'll see some of the same findings in rodents that we've seen with our -- with our STC platform and we will -- we'll report out on that as we generate more data.

And so with that really, I'll summarize on slide 36 and tell you that we have developed an effective and well-tolerated subQ-administered platform which is our GalNAc conjugate platform which has been translated in humans across our TTR program and our AT3 program. This Enhanced Stabilization Chemistry results in increased metabolic stability and that translates to higher liver exposure, improved potencies as I've shown you, increases in potency of about 10 fold from our previous platform, increased duration of effect which seems to be further increased as you go from rodents to non-human primates to humans where we see the greatest duration of effect and the [greater] potency and an overall general environment which we believe suggests that human have -- the most stability of our drugs in humans and that's really attributing the -- is a suggestion for why we're seeing this enhanced activity in humans relative to non-human primates.

And of course, in the early days that we have so far on tolerability, we really see no changes in tolerability with this -- within -- with this enhanced potency and enhanced stabilization platform and so we recognize that we now have a platform which we can translate across any target and across the whole variety of disease. And that really opens up the door for this whole new class of medicine.

And I guess with that, I will -- I will end. Happy to take questions.

QUESTIONS AND ANSWERS

Joshua Brodsky: Great. Thank you very much, Rachel. So, as Rachel said, we'll now open it up for Q&A.

(Operator Instructions)

And so Laurence, please go ahead.

Laurence Reid: Thanks, Josh. So, number of questions coming in. Thank you very much for people's interest. So, Rachel, why don't we start with this first question that we've had submitted and you touched them as in, in the presentation but if you could the question is do we anticipate that the increased potency of the ESC GalNAc conjugates that we see in humans versus non-human primates could be an AT3 results? Do we imagine now that will hold up as we get to higher levels of knockdown?

Rachel Meyers: So, that's a great question. Obviously, the best answer to that question will come when we get the data in clinic but everything that we know about the platform and the consistency and dose responses -- dose responsiveness of it both in non-human primate, as well as in human in other settings suggests to us that very likely we will see those same increases in potency and durability as we continue to dose escalate in this program.

Laurence Reid: Excellent. There are a couple of sort of related of questions here we're trying to look forward to the future of the platform. The first -- the first question is about really technology from siRNA. So, were there technologies from the siRNA acquisition that we think we can use to improve the ESC conjugates in the future?

Rachel Meyers: What we've learned from our siRNA colleagues is that they, of course, they've spent a lot of time understanding siRNA chemistry just as we have and there's been lots and lots of complementary data that we -- that we've come to understand. There's been lots of interesting new assays that they have spent a lot of time working on and we are hopeful that we can add to our own body of knowledge, the knowledge from siRNA that will help us perhaps even tease out more of an understanding of mechanistic understanding of our ESC GalNAc conjugates a little bit more about how they -- how they transit through cell, what are the enzymes that might be degrading these siRNAs and perhaps even -- they can help us develop some additional assays that will help us understand these differences that we're seeing between non-human primates and humans. So, we're quite excited about continuing to mine the siRNA data and expand on our platform.

Laurence Reid: Excellent. And a related question, where is Alnylam when thinking about non-GalNAc conjugates from the future and anything that you think is close to the [clinic]?

Rachel Meyers: Well, we love to think about alternative targeting strategies. It's one of the favorite things of the [folks] in research. At this moment, we don't have anything that's primed to going to clinic but we have lots of ideas, and importantly, we definitely believe that that the learnings that we've had from our ESC GalNAc conjugate will be extremely translatable to another targeting strategy. There's lots and lots of important things on the siRNA chemistry that we've learned over the last 5 years that will be directly translatable and should make that transition to that next delivery platform faster. Stay tuned.

Laurence Reid: Excellent. Good. Yes, good answer. So, stepping back a little bit, I mean, you did a beautiful job of walking us through the technology in some depth. But if you stand back and look at the overall landscape, question we've got in here is what advantages over other RNAi delivery platforms in the community do you see that the GalNAc platform really possesses?

Rachel Meyers: Yes, that's a great question. So, there's a few significant advantages. The first, of course, is that this is a relatively simple structure of the drug. So, it's single drug entity which is it's completely manufacturable and characterizable quite simply and so we can really understand everything about this drug, and it's highly water soluble. We can make it at a very high concentrations. We can deliver it subcutaneously and so that obviously has some significant advantages from the point of view of the patient and access to different indications that might not be available to an [IV] strategy, and really importantly, it's incredibly safe.

All the data that we have so far suggests that we really think very, very little by way of adverse reaction to this platform and so we now have a very simple to use, relatively straightforward to make, very potent, and very safe platform. And so we really think that holds it ahead of some of our -- some of our competitors.

Laurence Reid: Excellent, yes. Thank you. Here's a question and we get this question more than frequently currently given the significant advantages that you described this morning, so tell them -- tell our listeners please about our plans if any to develop a next generation TTRsc lead using the ESC GalNAc technology.

Rachel Meyers: Yes, that's a great question and, of course, as you might imagine, we have certainly developed ESC version of our TTR drug as I've described to you. You can start with that same sequence and apply some chemistry. So, we have a -- we have an enhanced stability version of the TTR compound and we're currently really evaluating the best strategy for introducing that [countdown].

Rigth now, we're pretty excited about ALN-TTRsc and marching it through the development. As I indicated, it is currently in Phase II and we'll continue to think about how best to introduce a potentially more potent version of that in the future.

Laurence Reid: Again, so branching out a little bit from what you talked about around the chemistry this morning. Great question coming here that we certainly thought about a lot over the years. So, the question is following, it seems that the GalNAc conjugates facilitate targeting for liver and uptake in the hepatocyte

cytoplasm, what do we know about how the siRNA gets out of the enzymes -- out of endosomes -- excuse me and what do we know about how much of the injected drug actually makes it into the cytosol of the hepatocyte?

Rachel Meyers: Yes. So, I'm probably going to disappoint you a little bit because I'm not going to completely be able to answer that question because unfortunately we don't know everything about that yet. We certainly know that drug does have to transit into endosomes and then get released into the cytosol and we know that that happens if -- as I showed you we have nice evidence of loading into RISC that supports that.

Exactly, why and how that happens? We really don't know. We do believe that having this Enhanced Stabilization Chemistry is really important enabling that we reaching out of the endosome because we allow the drug to be stable enough to survive for significant periods of time in the endosomes so that it can get out into cytosol.

From data that I showed you actually comparing levels of siRNA in the liver versus level of siRNA in RISC, we believe that about 1% of the drug that we're able to detect, at later times after dosing, about 1% of the drug that we are able to detect in the liver is actually bound up in RISC as a surrogate for what might be in the cytosol. So, there are certainly excess drugs which had potential to reach out of the endosome over time allow for additional rounds of loading into RISC and really giving us that sustained durable effect. But it would -- I would be lying if I didn't say that there's more for us to learn and understand about that -- about that mechanism.

Laurence Reid: Another related question, are there explicit mechanisms or components that you think you could add to that GalNAc chemistry to enhance the endosomal release?

Rachel Meyers: Yes. So, there is lots and lots of work that has gone on across the field in trying to do that because everybody recognizes that release from the endosome might be a key to improving potency and there are certain strategies that are endosome disruptive strategies of which are LNP has such a strategy and right -- with some of those lipids.

What we found so far is that we've really been able to -- we have not been able to come up with such a strategy that allows us to get that endosomal escape in a way that generates a really safe drug. And so while we can introduce very different chemistries that results in significant amounts of endosomal escape, we really haven't been able to find a strategy for doing that where we generate a drug that has the therapeutic profile that we're really interested in.

But if anyone has a great idea, please send it to us.

Laurence Reid: Let's just talk a little bit about the human setting, the clinical setting, couple of common questions that get asked here that have come back in from some of our listenters this morning. What, if any premedication, do you use in treating patients with GalNAc conjugate drug candidates?

Rachel Meyers: Yes. So, for -- importantly for our GalNAc conjugate platform, we require no premedication of any kind. It's a [aquid] soluble drug that we deliver in simple solution with no premedication. One of the additional beautiful features of this platform.

Laurence Reid: And then as we've been through -- some recent human studies, so in the AT3 study with the new ESC technology, of course, you described this morning, did you notice any cytokine induction or complement activation in the SAD Phase I study with ALN-AT3 that we recently reported?

Rachel Meyers: So, we have seen no evidence of cytokine or complement activation. In fact, we've seen no evidence at very, very high doses in any of our animals toxicology studies as I said up to doses of 300 mg/kg and importantly we have seen in non-human primates and importantly we have seen no evidence of death so far in our clinical studies either.

Laurence Reid: So, that was very much -- that was sort of [final] question about ALN-AT3 which, of course, includes the [ESC] chemistry to go back a little bit to our ALN-TTRsc. Can you comment on the -- on the ISR profile that we observed with ALN-TTRsc whether in volunteers or patients?

Rachel Meyers: Yes, so for our TTRsc program, we reported out at the end from our Phase I study which is in the healthy volunteers and we reported out this data last September and what we -- what we observed that it was -- it was quite generally well tolerated with no serious adverse events, no discontinuations, no clin path findings, no elevations in LFTs, and really no evidence of a proinflammatory effect. We couldn't see any cytokine elevation or [CRP] or increases in CRP.

And the one adverse event that we did note was a dose-dependent increase in erythema which was right at the injection site. It was -- it was quite transient and it only lasted a couple of hours and so we were pretty excited about the safety profile of that STC conjugate.

Laurence Reid: Excellent. OK. I think we'll take -- one more question here actually about IP. We'll take at least a way to wrap-up this morning, again, we thank [everybody] for their interest and participation. So, it's -- we talked -- we actually released this morning about [align us] of the 478 -- the Manoharan 478 and could you comment on the -- on the development of the technology that underlies that patent? Was that developed internally or is it part of the Merck estate?

Rachel Meyers: So, that is a consequence of all the work really that I just -- I just laid out for you which was an internal effort by our chemists and biologists here at Alnylam, a labor of love, I would say.

Laurence Reid: Excellent. Thank you. A lovely way to end. So with that, back to Josh to wrap-up, but once again, thanks from Rachel and myself for questions and interest this morning.

Joshua Brodsky: OK and I thank all of you for joining us for the RNAi Roundtable. We look forward to your participation next week as we discuss the progress that we're making with ALN-HBV in development for the treatment of hepatic B virus infection, and in the weeks that follow to discuss the topics listed on slide 38. In addition to these summer webinars, we also have a significant series of expected presentations of scientific and clinical data a number of meetings in the mid to late part of this year as shown here on slide 39.

So, this concludes today's RNAi Roundtable. Thank you all for joining us and have a great day.

Operator: Thank you, ladies and gentlemen. That now concludes your conference call for today. You may now disconnect. Thank you for joining and enjoy the rest of your day.