Corporate Speakers
- Barry Greene, Alnylam Pharmaceuticals, President & COO
- Benny Sorensen, Alnylam Pharmaceuticals, Medical Director - Clinical Research
- Cynthia Clayton, Alnylam Pharmaceuticals, VP - IR & Corporate Communications
- Anita Hill, University of Leeds, Consultant Hematologist

PRESENTATION

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 like to turn the call over to Cynthia Clayton for opening remarks. Cynthia, you may proceed.

Cynthia Clayton: Good morning, everyone, and thank you for joining us for our RNAi Roundtable to discuss the progress we're making with our program and development for the treatment of complement-mediated disease.

I'm Cynthia Clayton, Vice President of Investor Relations and Corporate Communications for Alnylam. With me today are Barry Greene, our President and Chief Operating Officer; Dr. Anita Hill, of the University of Leeds, and Dr. Benny Sorensen, Medical Director of Clinical Research at Alnylam. I will be turning it over to Barry shortly, who will provide you with a brief introduction, but first a few comments.

Today's event will end at about 10:30 a.m. Eastern time. We will be taking questions from you via the webcast. You may submit a question at any time by clicking the Ask a Question button located above the slide window on the webcast player. Barry will moderate a Q&A session with both Dr. Hill and Benny at the conclusion of their presentations.

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

Barry Greene: Thank you, Cynthia, and good morning, welcome everyone. I'm excited to be kicking off our RNAi roundtable for C5. I would especially like to thank Dr. Anita Hill for joining us on this call from Leeds.

So as you're aware, we presented a tremendous amount of data this year, particularly May and June, and we felt it would be helpful to recap those data and highlight the strong science, critical unmet need and the potential clinical development paths for many of our programs. This, in fact, is our fifth roundtable in this series.

So on Slide 6, let's initially focus on the progress Alnylam has made over the last several years. We believe we created a reproducible and module path to develop genetic medicines. Today,
particularly with our GalNAc-conjugates, if there is hepatic synthesized protein involved in the cause or pathway of an important disease, we can knock it down with a potent molecule that, thus far, are demonstrating a very broad therapeutic index.

As I'll share, our pipeline has been strategically driven by our 5 by 15 strategy, of pursuing targets with strong genetic validation for serious diseases with clear unmet need, robust biomarkers in Phase I, oftentimes, in fact, the circulating protein itself, definable and expeditious development path. And assuming the kind of positive patient impact we planned, we believe each of these programs will offer a significant commercial return.

Now as we turn to our pipeline chart, it's clear we have an emerging pipeline of potentially high-impact RNAi therapeutics. As you heard during the TTR Roundtable, patisiran APOLLO Phase III is progressing well and on schedule. For TTRsc, we'll have some very interesting TTR cardiomyopathy patient data to review in the fourth quarter as we prepare for the start of the TTRsc Phase III later this year. For complement, we'll talk more about that later today.

Now, all in all, we have 11 programs at various stages shaping up to be a very rich and, hopefully, medically high-impact pipeline. So for today, before I pass the call over to Anita, we're focused on ALN-CC5 for the treatment of a wide range of complement-mediated diseases starting with PNH.

So with that, I'd like to turn the call over to Anita. Dr. Hill?

Anita Hill^ Hello?

Cynthia Clayton^ Yes, we can hear you. Please, go ahead.

Anita Hill^ If we go to my first slide, I will be talking about paroxysmal nocturnal hemoglobinuria, or PNH, and give a brief overview, as well as the consequences of having this disease and why it can result in a high morbidity and mortality, and why therapeutics are therefore needed for patients with this disease.

On the first slide, you can see what was used to be called the triad of PNH. First of all, this slide shows the picture of the classical dark urine that patients may pass, but certainly, not all patients experience this. It is an acquired disease, so it can present at any age of life in any decade. So we are aware of looking for patients with this disease in all age groups.

PNH always arises on the background of a bone marrow failure. So these patients do have two disease processes that need often separate management. That bone marrow failure might be aplastic anemia, but has also been recognized in other bone marrow failure syndromes such as myelofibrosis and myelodysplasia.

We are most concerned about the complication of thrombosis, and that has conferred the highest risk of morbidity and mortality. But there are other organ damage complications that do occur because of the chronic complement activation that's unregulated.

Onto the next slide. The disease itself is caused by an acquired mutation in the PIGA gene in a hematopoietic stem cell, and that mutation results in a loss of the structure that you can see just above the cell membrane called the GPI anchor. That GPI anchor normally attaches more than 100 proteins to the cell membrane. However, it seems that for the majority of these proteins, it's not essential that they are closely associated to the cell membrane. But certainly, for the disease
PNH, it's very apparent that -- it is important that the complement regulatory proteins, CD55 and CD59, should be closely attached to the cell membrane. So the loss of these in PNH is what really confers and gives us the clinical manifestations.

Onto the next slide to describe the pathophysiology. So the first step in the process is an individual developing PNH is acquiring the PIGA mutation. And there are likely to be a fair number of people listening to this to today who have actually had a mutation in a PIGA gene in a hematopoietic stem cell. So there is a PNH stem cell fixing in the bone marrow. But the reason the disease is still there is because that is just one step in the process. The second step is also on top of this mutation acquiring a bone marrow failure syndrome, such as as demonstrated on this slide, an immune attack that can destroy the normal stem cells that allow the PNH stem cells to expand.

If there is then further clonal expansion, then you develop PNH red cells, PNH white blood cells and PNH platelets. And all of these PNH blood cells are lacking the CD55 the CD59 on the surface. So all of them are sensitive to the attack by complement. And this is what results in the features of the disease, as well as the complications.

Next slide. The diagnosis of PNH can be simply made by the gold standard investigation of flow cytometry, and this slide just shows some of the analysis that we do in our lab here in Leeds, using six-color flow to make the diagnosis. Most hematologists have access to this test quite simply, although we do have to ensure that we are doing the test accurately. Unlike this process that we use for other hematological conditions, in PNH, we're looking for the loss of proteins on the cell surface rather than an apparent phenotype that we do for our other hematological disease processes.

Next slide. We actually tried to look at the epidemiology of this disease a few years ago, and this just firstly shows a map of where I work in the U.K. And the Leed's teaching hospitals and university are based in West Yorkshire. The laboratory associated with my hospital is the only laboratory in this dark green area that runs the PNH screens for the whole of this population. So we looked back at the previous 10 to 15 years to see how many diagnoses of PNH we have made in this area.

Next slide. And you can see that from this study in the Yorkshire population, we estimated an incidence of 1.3 per million per year, with a prevalence of near 16 per million. And what's important to point out here is that these diagnoses were for any size of population of PNH cells. So they were from the very small, less than 1% presence of PNH cells, to that near 100% or 100%. If we extrapolate that incidence in prevalence to the rest of Britain, because there is no reason to suspect that the Yorkshire population is different, then you can see the estimation from this slide for who we predict would have PNH in Britain.

Next slide. This is why we want to find the patients with PNH. And we've looked at a survival curve more recently and, I think, disappointingly, for patients on supportive therapies only. So this is up to the year 2000, we saw that the survival of patients is still very poor, with 1/3 of patients dying within five years of diagnosis. And when I usually present PNH to hematologists, I compare this survival to worse than some of the hematological malignancies we look after. So although it's classed as a benign disease, it's survival is worse than, for example, chronic myeloid leukemia, which is why we should find the patients and then optimize their management and therapeutic strategies.
This cartoon tries to demonstrate why there is a high morbidity and mortality. The left-hand side of the slide shows the complement activation on a healthy intact red cell and how that red cell will be protected from that complement attack, specifically in humans by CD59 on the surface. The middle column shows a PNH red cell, which is lacking the CD59 on the surface. So when the complement system is active, this PNH red blood cell will rise in the intravascular system and release hemoglobin. This can result in anemia quite commonly, but not always, but also that complement attack, we must remember, is also occurring on platelets and on white blood cells.

The anemia, the white cell activation and the platelet activation, as well as the release of hemoglobin, consuming quite avidly, nitric oxide results in the clinical complications and symptoms. And these can have the impact on survival that you see.

Next slide. The first complication to mention is thrombosis. And this slide really illustrates many of the mechanisms of thrombosis that are thought to occur in PNH. But what’s essential is the complement activation. And this, I think, has been highlighted by our experiences by complement inhibition and the positive effect it’s had on reducing thrombosis rate.

Next slide. What was also previously underestimated was the degree of renal dysfunction that patients with PNH can experience, and it’s something that we now monitor for very carefully in all patients with this disease process. The causes, again, of the chronic kidney disease is the intravascular hemolysis and also thrombosis. And if, therefore, these consequences are prevented, then we hope to reduce the incidence of chronic kidney disease.

Next slide. We’ve also shown that the intravascular hemolysis and the thrombosis risk in PNH can contribute to the third complication which can impact mortality, which is pulmonary hypertension. And using noninvasive measures, because of the risk of right heart catheterization, we’ve shown that approximately half of patients with PNH can run the risk of long-term raised pulmonary pressures, which ultimately can result in right heart failure and could contribute to an early death.

Next slide. Many of these complications, as highlighted in this paper, can be subclinical or near-subclinical with very few symptoms. And again, an important learning point, therefore, for managing hematologists has been to monitor for these complications very carefully. We’re fortunate in the U.K. to have a national PNH service, so we can ensure that these complications are screened for and managed appropriately. But elsewhere in the world, individual hematologists have to be made aware of these potential problems, so that the patients don’t have an early death due to them. And often, as you can see from this slide, the average age of many patients are in their 30s and 40s. And in order for us to have an impact on their life expectancy, we need to manage these complications early.

Next slide. This slide just lists some of the supportive measures that we have available to us, historically. And I won’t run through them all now, but just to say that these supportive measures clearly have no impacts on the mortality of the disease, even in recent years when we had optimized transfusions and anti-coagulation.

Next slide. Transplantation is still the only curative strategy. However, despite the improvements in transplant rates in patients with aplastic anemia, for example, the mortality for patients with PNH still remains at near 50%. And therefore, certainly, our recommendation in the U.K. is that when newer complement inhibition therapies are available, the indication for bone marrow transplantation is only the bone marrow failure. For example, severe aplastic anemia or
transformation to MDS or AML. And we would, otherwise, use the complement inhibition therapies that we have available to us.

Next slide. So to talk about complement inhibition, I just wanted to come back to this cartoon. You can see from this, probably, a couple of strategies that we could take in PNH to try and prevent the high morbidity and mortality and the symptoms that the patients experience. One strategy would be to try to replace the complement regulatory proteins that are missing, for example, the CD59. And another strategy would be to target the complement system itself.

Next slide. We tried, firstly, to actually replace the CD59. If we just click on again, we achieved this with a compound called Prodaptin CD59 and showed in [new] remolds that we could actually anchor recombinant human CD59 to the self-service, and the next slide shows the inhibition in, in vitro assays of these blood cells once they had been coated with Prodaptin CD59. However, this therapy would've been, obviously, very specific for PNH alone, and development of this stopped when we heard and started using the drug eculizumab, or Soliris, in the pilot study in 2002.

Next slide, please. You can see here how it's the terminal complement activation that results in the features of PNH. And if we just click on again a couple of times, we can see where the points of action of eculizumab is. By binding to C5, it presents terminal complement activation, and we have shown, through our studies in recent years, the impact that this can have in significantly reducing thrombosis rate, improving renal function and improving pulmonary pressures.

If we click on again, the point to make is that the proximal complement system does remain intact and we have, therefore, not seen an increase in bacterial species apart from knowing that there is an increased risk of neisseria meningitidis alone because of the lack of terminal complement. So the fact that the proximal complement system remains intact is important for preventing all other infections.

Next slide. Eculizumab that we have used, we know it's a monoclonal antibody and it has been shown to be effective in preventing intravascular hemolysis. This drug itself is an intravenous administration with a five-week loading period, followed by two weekly infusion thereafter. Again, in the U.K., we're fortunate that we have home [care] provision of these infusions to try and minimize the impacts in hospital visits a patient may need. And for our patients in the U.K., we have no dose-related reactions or premedication required.

Next slide. This drug has shown that it is very effective in preventing the intravascular hemolysis, as demonstrated by the significant reduction in LDH, the best marker for monitoring intravascular hemolysis. You can see though, that the LDH remains at or just above the upper limit of normal.

Next slide. There is a significant reduction in transfusion requirement, with two thirds of patients becoming transfusion-independent. But this does mean that a third of patients may remain transfusion-dependent, and there are three principal reasons for this.

The next slide, and if we just click on again, you can see how, in a small number of patients, this dose of eculizumab that we use as a standard in PNH may not be sufficient and there can be a breakthrough of the complement blockade. This is being managed by increasing the dose of eculizumab for these patients.
Next slide. This slide is just to remind that the patients also have an underlying bone marrow failure. So one other reason they may need continued transfusions is because their bone marrow failure needs separate management, either with immunosuppressive therapies or with, I've shown here, erythropoietin injections.

And the next slide is just to remind the fact that C3 remains intact, which is important for optimization of bacteria. But if we click on twice again, you can see that for patients on PNH, there's also effectively an optimization of red blood cells. And this can result in an extravascular low level hemolysis.

And if we just look at the next slide again, we showed that it is just the PNH cells which are coated in C3. Despite the fact that some patients may still need an increased transfusion -- sorry, continued transfusion requirements, we do see, if we see on the next slide, that despite this, so it's still a significantly improved survival for patients on eculizumab because of the terminal complement inhibition, showing the effectiveness of this strategy in patients with PNH.

So finally, I hope that describes how PNH is predominantly, a complement-mediated disorder, but there are two disease processes in patients with this condition. Eculizumab has shown by proof of principle how terminal complement inhibition have significantly improved survival. And I just listed some of the strategies where we will be looking at developments in the future of how we can further improve this already dramatic improved survival for these patients, such as making administration easier, reducing the frequency of administration, and I'm sure, for all health services, if we can have an impact on cost.

Thank you.

QUESTIONS AND ANSWERS

Barry Greene^ Thanks, Anita. That was a wonderful overview of PNH. We have some questions that are coming over the transom. Let me direct the first one to you. So the first question is, there are a large number of patients already on eculizumab, and we've heard from some companies that it's nearly impossible to run clinical trials in PNH. Given the large percent of these patients, Anita, how would you address clinical trials here?

Anita Hill^ Thanks for the question, some companies -- other people may not be aware of how we work in the U.K. As I said, we're fortunate to have a national PNH service. And our PNH patients are centralized. So for example, where I work, in the Leeds center, we see over 300 patients with PNH every year, and approximately half of these patients are on eculizumab. So that gives us well over 100 patients who are not. Now that's because often, we're monitoring them, and therefore, starting therapy as and when they need it. But there is still, therefore, a very good pool of patients in whom we can certainly perform clinical studies if needed.

Secondly, taking your product in particular, there is a very different mode of action of your product compared to others that we have come across in development. And actually, I could see an overlap in studies that we could do in both treatment-naive patients, but also in trials for patients on therapy itself.

Barry Greene^ Great. Thank you for that. Another line of question has to do with achievement of clinical benefit with a synthesis inhibitor. So the question said, "It's clear you can knock down C5 in the liver, but we've heard that you need to knock down 100% of C5 in the liver and in other
tissues that it synthesized. So the question is how much knock down do you need for C5 to achieve clinical benefit?"

Anita Hill\footnote{Anita Hill} Again, a good question, and one that we haven't previously explored. I can understand that we would want to try and abolish all C5 activation, but I think the way we would do this initially, and we'd probably be quite keen to do in our laboratory, is to take the serum of some of the primate studies that have been done and, certainly, the healthy volunteers, and do some in vitro analysis and see if there was any C5 left in the system that could lyse PNH red blood cells.

So if we did those, we could then try and deduce whether there would be a clinical efficacy or benefit to the patient. And from my understanding, again, limited, but I think a lot of C5 is produced from the liver, and your data shown previously have shown that you're getting a near 98% reduction in C5 levels. So just seeing whether that is sufficient to prevent the lysis that we see in PNH, we should be able to tell quite early on from in vitro studies.

Barry Greene\footnote{Barry Greene} That's great. Well, thank you very much. I guess we've got time for one other question before we turn it to Benny, and then we'll get back to the Q&A at the end. So question, how would some of the other approaches, for example, targeting [lectin] or alternative pathways to treat PNH, compare with eculizumab or the Alnylam RNAi CC5 approach?

Anita Hill\footnote{Anita Hill} Well, I think what eculizumab has done by docking terminal complement, is follow what we knew from previous literature. So when we were doing the pilot study, for example, back in 2002, we explored a lot about the effects of terminal complement inhibition. And that looks like the safest area to target the complement system C5 or beyond.

Proximal to C5, any patients who seem to have proximal complement deficiencies can have quite significant health problems autoimmune diseases, recurrent pyogenic infections, renal dysfunction. And so, I would have some anxieties about the effects of targeting other areas. I think our experience, and we have turned to immunologists for some of this, if you target C5 or beyond, we seem a little more reassured by what the long-term effects might be.

Barry Greene\footnote{Barry Greene} Well, thank you. We'll probably have some other questions after Benny's talk as well, but let's turn it to Benny for the overview of the ALN-CC5 program. Benny?

Benny Sorensen\footnote{Benny Sorensen} Thank you very much, Barry. And our first slide, [Josh]. So our complement program is really targeting a variety of complement-mediated diseases, all characterized by excessive complement activity. This include PNH, as just described in detail by Dr. Hill, but also atypical hemolytic uremic syndrome, neuromyelitis optica, membranous nephropathy, myasthenia gravis, and to this list, we can also add renal graft rejection. And we strongly believe that new therapeutic options are needed here, and particularly a subcutaneous delivery that would allow more tolerable treatment regimens for patients, but also utilizing the mechanism of action of RNAi to achieve more consistent level of efficacy.

And finally, we do believe it's important to reduce access barriers to treatment and optimal dosing.

Complement C5, as also just recently described here, it really plays a key role in the complement system. And C5 is a genetically-validated target. Thus, being the key component of the terminal pathway of complement, C5 cleavage releases C5a and it initiates the establishment of the membrane attack complex. C5 deficiency is associated with minimal complications. There are
multiple C5-deficient animal models with limited physiological abnormalities. Although, there is this susceptibility to increase the neisserial infections. The majority, if not all of the C5, is expressed in the liver and circulates in plasma.

In addition to being genetically-validated, C5 is a clinically-validated target in the way that eculizumab as an monoclonal antibody targeting C5 has proven efficacious and approved for the use in PNH and aHUS, and also a variety of other Phase III clinical trials are ongoing.

In particular in PNH, an approximately 80% or more inhibition of hemolytic activity has been associated with their clinical benefit. We do believe though that there could be potential advantages in inhibiting the synthesis of C5 versus a protein-binding approach.

Now ALN-CC5 aims to target a variety of unmet needs in complement-mediated diseases, including efficacy, safety, convenience and access. With efficacy, we believe that the inhibition of endogenous C5 production via RNAi can provide more consistent level of efficacy, and particularly, in the presence of fluctuating C5 levels or C5 levels elevated secondary to inflammation. Also, it would allow the -- allow to be efficacious in the presence of, for instance, proteinuria or if there's a need for concomitant plasmapheresis. And finally, this approach will be effective in patients resistant to eculizumab.

Safety is key, and we believe that improved tolerability versus standard of care is an important unmet need in, particularly, to reduce the risk of IV complications, but also for complement-mediated diseases where immunosuppression is still standard of care. Reducing that would be an advantage. And as just addressed by Dr. Anita hill, it's important that we keep on optimizing the convenience to reduce the overall treatment burden of patients. And we can do that by lowering the burden of venous access, enable less frequent and less time-consuming treatments, and for some complement-mediated diseases, reduce need of plasmapheresis.

And finally, access. It's key to improve access to patients needing C5 inhibition. Thus, lowering payer access barriers is important, and also expands the opportunities to use C5 inhibition in patients currently not being offered or considered for them.

And finally, the mechanism of action allows the synergistic use of other C5-neutralizing regimes.

Just ALN-CC5 here, in a nutshell, is a subcutaneously-administered GalNAc-conjugated small-interfering RNA that targets C5. The GalNAc directs the double-stranded small-interfering RNA to deliver by associating with DSL or glycoprotein on the surface of hepatocytes is being endocytosed and released in the hepatocyte, where it associates with the RISC complex, the RNA-inducing silencing complex. And here, the [endosome] string will form a -- will detect the complementary C5 messenger RNA and facilitates its degradation. Degrading the messenger RNA will reduce translation and production release of C5 protein.

We're using the enhanced stabilization chemistry for our potency and durability, and as you can see on the right side here, a weekly subcutaneous dosing results in potent and sustained suppression of C5 levels. And in these mouse experiment, the ED50 was 0.25 milligrams per kilogram.

Very importantly here, we get a very robust knock down of serum C5 with subcutaneous dosing in nonhuman primates. We've done experiments with 5 milligrams per kilogram irrespective of a loading dose. We achieved up to 98.7% silencing of C5. And based on our human translation of the enhanced stabilization chemistry GalNAc-conjugates, we expect a similar efficacy at less than
1 milligram per kilogram weekly in men. And just one click, I would like you to emphasize on the consistency of this C5 knockdown. And here, you can see, individual curves from animals, and please notify the consistency and steady-state knockdown we see of C5 here.

Now one thing is the elimination of C5 from plasma, but what's important is to inhibit hemolysis and get a clinically-meaningful inhibition of hemolysis. We know from studies that have been conducted by Dr. Hill and other colleagues that hemolysis inhibition to approximately or less than 20% of normal, is associated with clinical efficacy in both PNH and aHUS. So we don't see any evidence that you would need more than 99.99% hemolytic activity inhibition.

I think what's important to emphasize here is that in the initial studies that we've done with the PNH, we did see some people experiencing breakthrough and incomplete effects of eculizumab. Now, in more kind of clinical field studies on your right with atypical aHUS, you can see that's also the case when eculizumab is used out in the clinic and monitored here in a sheep red blood cell hemolysis assay where you see some partial effects of eculizumab, at least hemolysis above this 20% threshold that we have put.

With ALN-CC5, we achieved very potent and complement activation -- activity inhibition. Both classical and alternative pathways of complement activity is greatly reduced in serum from nonhuman primates treated with ALN-CC5, we achieved up to 96.8% inhibition of complement alternative pathway activity, and up to a 91.3 inhibition of hemolysis. And I think what's important to emphasize here is this consistent clamped inhibition of serum hemolytic activity during dosing and between dosages.

ALN-CC5 has also been shown to be equivalent in efficacy to an anti-C5 antibody in a mouse model of collagen antibody-induced arthritis. And I think what you can appreciate here is that there's really absolutely no difference between the clinical disease activity achieved when an anti-C5 antibody targeting a neutralizing mouse C5 as compared to ALN-CC5.

Well, based on this, we believe that there are little or really no roles to locally produce C5. What's very important is that with ALN-CC5 and the technology of RNAi, we achieve robust C5 knockdowns also during inflammation. And in our study in the collagen antibody-induced arthritis, we did see a considerable up-regulation of serum C5. However, that kind of fluctuation or up-regulation of C5 was not seen in the animals treated with ALN-CC5, where we saw, literally, no C5 fluctuation whatsoever.

Finally, this technology, ALN-CC5, allows for a potential C5-neutralizing sparing effect as well. So if we -- when we neutralize a -- when we reduce C5 with 95%, the use for a C5-neutralizing antibody would reduce up to twentyfold. And we're speculating that lower serum C5 levels also could increase the half-life of a monoclonal antibody. It does -- so this opens an opportunity for a anti-C5 monoclonal antibody sparing approach as we go forward.

In summary, we -- our preclinical data has shown a robust knockdown of serum C5 and inhibition of complement pathway activity in a nonhuman primate with subcutaneous dosing. Based on our enhanced stabilization chemistry platform, we do believe that we will achieve a similar effect with less than 1 milligram per kilogram in humans. Knockdown of liver-derived C5 also showed therapeutic efficacy in this mouse arthritis model, and that efficacy was equivalent to an anti-C5 antibody treatment.
Importantly, the knockdown we are achieving is consistent, even in the presence of an inflammation. And we believe that the RNAi approach can reduce anti-C5 monoclonal antibody cost and dose frequency if used as a sparing approach as well.

And finally, we haven't talked about that in detail, but we have a wide therapeutic index, up to 250 milligrams per kilograms per week has been well-tolerated in our initial safety studies in both rodents and nonhuman primates.

I think what's important now to kind of talk to is, where do we see the potential clinical indications for ALN-CC5 going forward. And when we list the variety of the complement-mediated diseases, we believe there are significant unmet needs that remains in these disorders. If we start with PNH, we believe that a major unmet medical need here is that there are still patients that are requiring considerable dose adjustment and dose increase of monoclonal antibody to get a consistent efficacy. We also believe that the access to treatment here can be improved, so that all PNH patients that could benefit from C5 inhibition will be given that opportunity. And we believe that the convenience aspect of treatment here is important to improve getting a treatment that's more convenient and less time-consuming.

For the other diseases here, atypical aHUS, it's the same story with the dosing of monoclonal antibodies and also the access. And for atypical aHUS, some of these patients are requiring concomitant plasmapheresis, and that may be difficult if you are undergoing treatment with a monoclonal antibody.

In myasthenia gravis, again, tolerable treatment for refractory patients is a major unmet need, and also, it reduced disease progression and where immunosuppression is standard of care, you get a reduction, and that is important.

In NMO, it's the reduction in number and severity of attacks that's important; improved tolerability here versus standard of care; and also these patients occasionally require plasmapheresis, and reducing the need for that would be an advantage.

And finally, membranous nephropathy, it's -- we see a major unmet medical need here, inducing sustained disease remission. And also offer a treatment that can -- that are -- that can resist rapid filtration by the kidneys. And again, here, tolerability versus standard of care is crucial. That's a huge use of immunosuppression in membranous nephropathy, which is associated with some nasty side effects.

The potential targets of patient segments that we are looking at here is really very broad. We believe that there is a total of approximately 135,000 patients suffering from complement-mediated diseases. And of those, approximately 7,500 will be suffering from PNH and have PNH with a variety of symptoms that justifies treatment with a complement-mediating treatment. Also patients with atypical aHUS, we believe, that there are 5,000 patients with clinical significance uremia that could benefit. And there's a small fraction of patients with myasthenia gravis suffering from severe refractory MG. We estimate that to be approximately 7,500. We believe all patients with NMO could benefit from treatment with complement-mediating treatment. That would be 20,000 patients. And finally, patients with membranous nephropathy with persistent proteinuria, approximately 6,000 patients could benefit from our treatment.

So in summary, we believe that ALN-CC5 offers several commercial advantages. We think we can develop ALN-CC5 as a differentiated product with subcutaneous dosing and that could optimize disease management. We believe that there are multiple target patient segments that
could benefit from treatment, and we believe that the value of ALN-CC5 is strongly supported by pharmacoeconomics and there is a significant opportunity for global expansion.

This is a summary of our clinical development plan outline and it's really a broad-based development plan to maximize the product opportunity. Phase I, II study will be in healthy volunteers, and later on, with patients with PNH, targeting to achieve a proof-of-concept. That study will be followed by an open-label extension study for PNH patients and we will then, in parallel, conduct a series of studies targeting other complement-mediated diseases. The Phase I, II and open-label extension in PNH will be followed by a registration studies in PNH patients. And as you can see here, we have listed the other indications we believe we will be able to go into as part of our overall clinical development plan for ALN-CC5.

In summary, C5 knockdown with ALN-CC5 can provide very consistent level of efficacy. We believe it can overcome challenges of a C5-neutralizing approach by nullifying variation in C5 levels and also have advantage in other situations, such as in renal impairment or if there's a need for concomitant plasmapheresis.

The subcutaneous administration is worth emphasizing here as it offers significant advantages to frequent IV infusions and also in-hospital IV infusions. And so far, proof-of-concept has been achieved in various preclinical experimental settings and we are on-track for CTA filing in late 2014, and we expect initial data mid-2015. We believe that both PNH, but really, the variety of complement-mediated diseases represents a very attractive commercial opportunity and this applicability across broad segments of complement-mediated disorders with potential to address multiple significant unmet needs.

Our ambitious broad-based development plan is really to maximize product opportunity and aims to get this new treatment options to patients as soon as possible. Thank you very much.

Barry Greene^  Thanks, Benny. That was a tremendous overview of ALN-CC5. We're going to turn now to Q&A. Rather than read every question, I'm going to try to block some of the Q&As and general question. There's a number of questions about consistent efficacy, and they -- on Slide 45, you referenced more consistent efficacy. Can you explain it further? Does this have to do with the PK challenges of monoclonal antibodies versus synthesis inhibitors, or proteinuria or plasmapheresis? Can you help us understand the consistent efficacy claim better?

Benny Sorensen^  Yes, so consistent efficacy. I think the key here is we know that C5 fluctuates. It fluctuates under normal circumstances and in, particularly, fluctuates during an infection and inflammation. Increases in C5 is potentially jeopardizing the neutralizing effect of a -- at the monoclonal antibody. And with ALN-CC5 and the RNAi approach, as you can see on the data we have, we completely eliminate that C5 fluctuation. Thus, we are excluding the variation in C5 as a potential risk of either occult or avert hemolysis. So really, it's down to nullifying that fluctuation in C5. That's one aspect that could give more consistent efficacy.

I think the second aspect is in some disorders like, for instance, membranous nephropathy, membranous nephropathy is characterized by the establishment of -- the activation of complement in the basal membrane in the glomerulus of the kidneys. And as a result of that, you get an excessive proteinuria, and that proteinuria will eliminate not just but albumin, but other proteins, including a monoclonal antibody. So in that case -- so reducing C5 added at its source in the liver kind of excludes the risk that the treatment of neutralizing C5, peripherally, is kind of -- we avoid that fluctuation and avoid the risk of diluting the monoclonal antibody.
Barry Greene: I guess a follow-on from that. There's a number of questions here. And maybe Anita, you can comment first on this. How many of your patients are indeed on concomitant plasmapheresis that are also on treatment?

Anita Hill: That question probably doesn't apply to our because practice because that will be for the aHUS population. For the PNH patients, plasmapheresis isn't a therapeutic strategy. From my limited experience with our renal team here in Leeds on aHUS, for the patients who are effectively treated with eculizumab, it was one of the major plus points was that they could discontinue plasmapheresis. So I'm afraid, I think a nephrologist might be better-placed to answer that question.

Barry Greene: I got it, thank you. And Benny, so why would an RNAi therapeutic not have an issue that an antibody has with concomitant plasmapheresis?

Barry Greene: Well, again we are eliminating C5 from its source. So by reducing the production of C5, you won't have a problem with having another protein circulating that could be eliminated by plasmapheresis. So -- and neutralizing antibody could be eliminated by plasmapheresis, so by using RNAi to reduce the production of C5, you allow for concomitant plasmapheresis to take place.

Barry Greene: Great. There's a number of questions about PNH and some of the other indications. And I guess, the summary is, Benny, can you explain your further thinking on starting with PNH versus some of the other diseases where because of proteinuria or other issues, you might have an advantage? Why this order?

Benny Sorensen: Okay. So I think the main reason for really starting with PNH is, PNH offers a fantastic opportunity to get a very early read on efficacy. So PNH, as you -- I'm sure that Anita will help me here, but PNH is characterized by the significant increase in LDH. And achieving a sufficient and efficacious inhibition of complement and hemolysis will pretty momentarily reduce LDH. So it will give us a very early, very prompt read on the efficacy of ALN-CC5.

Also by having these collaborations with Anita and other KOLs in this area, we feel very confident that we can actually conduct both Phase I, II and III studies in PNH patients. And we believe they have still a considerable unmet need that we can fulfill. So a variety of reasons is why we believe PNH is the right first population to target. Technical reasons, we get an early read and there's still tremendous unmet need that we can mitigate with ALN-CC5.

Barry Greene: Great.

Anita Hill: And one thing I will just add, if I may, to the answer.

Barry Greene: Please.

Anita Hill: When PNH is probably one of the most pure complement-mediated diseases and it doesn't have many of the other factors that some of the other diseases may have. Obviously, aHUS is another complement-mediated disease, but it doesn't have the clear diagnostic criteria that PNH has. And so is, therefore, I think to do the studies in PNH, is, certainly, clinically the -- as Benny said, the actual efficacy will be apparent much earlier on.

In other conditions such as myasthenia gravis and NMO, we don't know what other factors might have an interplay, but we certainly know the pure complement effects that occur in PNH.
Benny Sorensen: Thanks, Anita.

Barry Greene: That's very, very helpful. So there's a number of questions about ALN-CC5 as a mono therapy or an antibody sparing therapy. So how are you thinking about it and how might the data steer you to decide whether it's a standalone or whether it's an antibody sparing approach?

Benny Sorensen: You know what as we -- as you can see in our preclinical data so far, we have a lot of confidence that this can become standalone. So the first approach is not to try to develop a clinical development plan that is very focused on antibody sparing regimes. We believe we can be efficacious as standalone, and that is what we target to prove. Then there may be investigators that could be interested in further working on either synergistic effects between ALN-CC5 and neutralizing agents and/or antibody sparing regimes.

And I think, we will take that later on. But first and foremost, our pre-clinical package is solid and it is generating confidence that we would be efficacious as standalone, and that's what we're targeting initially. And then later on, we can find out the need for establishing also antibody sparing regimes. There's no doubt that it can be achieved. We have preclinical data to show that you can probably reduce the need for a monoclonal antibody with up to twentyfold. And most likely, you also increase the interval between treatments. So that's -- it's a nice additional option to have, but in the beginning we are post going as a standalone.

Barry Greene: Great. I think we have time for one more question before we wrap it up. So eculizumab has orphan designation, will that be a hindrance to ALN-CC5 in achieving approval in commercialization?

Benny Sorensen: It's almost a question to you Barry, but so my answer to that would be no. It's not a hindrance. We are -- we definitely -- it's difficult -- a different mechanism of action and [we had] different molecule, different -- a different set of opportunities, I think. So no, I don't see that at all.

Barry Greene: And Anita, maybe you can comment on the desire that those in U.K. might have in offering a different therapeutic approach to patients?

Anita Hill: Absolutely. I mean, we, obviously, have had experience now with the intravenous nature of eculizumab for 12 years with some of our patients, and it is still well-received by many of them. But the frequency of the administration, the impact on the life is something that if we can improve, we would certainly want to. We are always trying to improve how we can manage our own patients. And so if we can offer longer interval between infusions or injections, and certainly, subcutaneous injections, this could have a huge impact, not just for the patient, but, obviously, for health resources as well because it would reduce, again, the need for nurses being sent to the patient's home or being used in the hospitals.

So I think anything that can help develop the welfare of the patient in the long-term is what we're looking for.

Barry Greene: Terrific. Thank you very much, Anita, and thank you, Benny.

I'm now going to turn to Slide 60 to wrap up. I thank everyone for dialing to the ALN-CC5 conference call, and I'll highlight that we have a number of upcoming RNAi Roundtables. On
August 14, we have a Roundtable on ALN-PCS Sub-Q for the treatment of hypercholesterolemia. That should be very interesting. And a broad discussion about not only on PCS Sub-Q, but the number of antibodies being studied in that disease as well.

On August 20, ALN-AAT for the treatment of alpha-1 antitrypsin deficiency-associated liver disease will be held. And then on August 21, the next day, the treatment of hepatic porphyrias with ALN-AS1 will be held. And as always, you can find, replays on Alnylam's website with Capella.

As we've talked about in our conference call and our Roundtables, we have a very data-rich fall coming up. And as you can see on Slide 61, we have meaningful preclinical and clinical data being presented in September, October, November, and December. And we'll get up more information out about this in the weeks and months to come.

With that, I'll highlight the speaker bios in the background, and I want to thank everybody for dialing in and appreciate all of your thoughtful questions. Bye.

Cynthia Clayton^ Thanks, everybody. This concludes our RNAi Roundtable for today. The replay slides and transcript will be posted on Capella, as Barry said, later today. And tomorrow afternoon, we'll be hosting our ALN-PCSsc Roundtable, and we look forward to your participation in that as well. Thanks and have a great day.