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ALNY - 2016 RNAi Roundtable: ALN-CC5 for the Treatment of Complement-Mediated Diseases Call

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PRESENTATION

Operator

Thank you, ladies and gentlemen for joining today's RNAi Roundtable. (Operator Instructions)

I would now like to turn the call over to Christine Lindenboom for opening remarks. Christine, you may proceed.

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

Good morning, everyone, and thank you for joining us for our RNAi roundtable to discuss the progress we are making with ALN-CC5 in the development for treatment of complement-mediated diseases. I'm Christine Lindenboom, Vice President of Investor Relations and Corporate Communications at Alnylam.

With me today are Jeff Miller, Vice President, General Manager of the ALN-CC5 program at Alnylam; Anita Hill of the University of Leeds; and Pushkal Garg, Senior Vice President of Clinical Development at Alnylam. I will be turning the call over to Jeff shortly, who will provide you with a brief introduction, but first a few comments.

Today's RNAi Roundtable will focus on our ALN-CC5 program as the third in a series of roundtables that we are hosting the summer and early fall. Today's event will end at approximately 12 PM Eastern Time. Jeff will moderate a web-based Q&A session with our speakers at the conclusion of our presentation and you may submit a question at any time during the webcast by clicking the "Ask a Question" button located above the slide window on your webcast player.

As a reminder, we will be making forward-looking statements and encourage you to read our most recent SEC filings in order to have a more complete discussion of our risk factors. And with that I will now turn the call over to Jeff.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP & GM, ALN-CC5*

Thanks, Christine; and thanks to everyone for joining us today to hear about our ALN-CC5 program. We have a very interesting program and, in particular, we are grateful to have Anita Hill join us to provide an overview and share her perspective on PNH.

As all of you know, Alnylam is the industry leader in RNAi therapeutics. It's what we've focused on since our founding in 2002 in the context of advancing RNAi therapeutics as a whole new class of innovative medicines.

RNAi is a powerful approach for gene silencing that harnesses a natural and catalytic mechanism. RNAi therapeutics have the potential to silence or down-modulate the production of any protein coded by any gene in the genome.

Through Alnylam's efforts, RNAi is a clinically-validated approach. There are multiple programs in our pipeline across multiple indications and disease settings in which we've demonstrated robust knockdown of the target gene in humans.

Alnylam has developed a pipeline of products focused in three strategic therapeutic areas, or STArs. These are the genetic medicines, cardiometabolic diseases, and hepatic infectious disease representing a range of disease opportunities from the rare to the common to the global.

You see here on slide 8 it shows our current pipeline organized by STAr. We currently have 10 programs in active clinical development. Two of these programs are in Phase 3 and a third is slated to enter Phase 3 trials in 2017.

The focus of today's roundtable is on ALN-CC5, our RNAi therapeutic in development for the treatment of complement-mediated diseases.

Now turning back to the agenda. Next we will hear from Anita Hill, who will provide an overview of PNH. We will then have Pushkal share the most recent clinical experience with ALN-CC5 and our current thinking on next steps. And I will share some results from a survey we conducted to explore physician sentiment on the unmet needs in PNH and then we will end with a Q&A session.

Throughout the presentation, as Christine mentioned, please remember to submit any questions you may have. You can do so by clicking the "Ask a Question" button located above the slide window on the webcast player.

So with that I'd like to introduce Dr. Anita Hill from the University of Leeds, who will provide an overview of PNH and describe the unmet needs in that clinical setting. Anita, turn it over to you.

Anita Hill - *University of Leeds - Honorary Senior Lecturer & Consultant Haematologist, Leeds Teaching Hospitals NHS Trust*

Thank you, very much. I'd like to start off with just giving a background of the disease of PNH and, therefore, why complement therapeutics have had a role to play in managing patients.

On slide 12, we first see the GPI anchor. The disease PNH occurs because of an acquired mutation in the PIG-A gene that results in a loss of this GPI anchor on the surface of cells. This results in a loss of proteins, most significantly in PNH the loss of CD55 and CD59.

If we move to the next slide, if we have a PNH stem cell in the setting of a bone marrow failure condition, such as aplastic anemia, where we believe there is an immune attack of normal stem cells, these PNH stem cells now have a survival advantage and they are able to grow in the setting of a weakened bone marrow. These expanded PNH cells can, therefore, go on to produce PNH red cells, PNH white cells, and PNH platelets.

And because they lacked those complement-regulatory proteins, CD55 and CD59, they are easily attacked, either activated or lived, by the complement system, resulting in the clinical manifestations that we see in PNH.

We looked at the PNH population in our county of Yorkshire in Great Britain. Leeds Teaching Hospital is based in West Yorkshire and the laboratory in this hospital is the laboratory that will test for PNH for the whole of the Yorkshire County of Britain.

We, therefore, on a population study saw that the incidence of PNH was approximately 1.3 per million per year, with a prevalence of approximately 16 per million. So, in Great Britain, we would expect to have approximately 900 patients with PNH cells.

The reason we need to find patients with PNH is because of the surprisingly high mortality for a disease that has often been called benign. But we can see from this survival curve that actually it is worse than some of the hematological malignancies we look after, such as chronic myeloid leukemia. Therefore, management strategies for PNH are very important because this -- for a patient with an average age of -- in their 30s and 40s, we need to be improving to give a survival advantage. Here we can see a third of patients may die within five years of diagnosis.

The reason for the high mobility and mortality is the lack of those complement-regulatory proteins, and this cartoon illustrates the hemolysis that occurs because of loss of CD59. And what the slide does not show is that the complement activation is also occurring on white blood cells and platelets, conferring the significant risk of thrombosis, which is the leading cause of mortality.

However, other causes of mortality will include renal failure, right-heart failure from pulmonary hypertension. And we shouldn't underestimate the impact that the symptoms have in terms of being able to work or live (technical difficulty) more lives. This is the reason we have a high morbidity and mortality.

The slide shows the strategies that were available prior to 2007 and we can see that the supportive measures had no impact on the mortality of the disease. Transfusions could transiently improve the anemia, but we found that patients still were severely symptomatic. Anticoagulation also have a major risk and indeed we saw deaths due to intracerebral hemorrhage due to anticoagulation.

Immunosuppression only has a role in the setting of bone marrow failure and not for the treatment of PNH.

Transplantation does remain the only curative strategy. However, the survival for patients with PNH undergoing transplant is still very worrying with a 40% to 50% mortality. And in these studies the average age of the patients undergoing transplant is just 28 years old. And, therefore, when the complement inhibitor therapies are available, we do not recommend transplantation for PNH; that the indication of transplant should always be for any underlying bone marrow failure that fulfills the indications for transplantation.

So we know that the loss of CD55 and CD59 results in PNH and we to date have the licensed therapy eculizumab. And with eculizumab we have demonstrated (technical difficulty). With eculizumab therapy we have seen a reduction in intravascular hemolysis, as measured by the LDH, and here we can see the LDH has fallen to or just above the (inaudible) normal after one or two infusions of eculizumab. And this has been repeated in many studies.

For those patients who were transfusion dependent before receiving eculizumab -- and patients do not need to be transfusion dependent -- but those who were, two-thirds become transfusion independent. That does mean one-third may still require transfusions.

In this group, we still see a significant reduction in the number of transfusions and the commonest reason for transfusions in this group are the bone marrow failure condition that allowed PNH to expand and possibly some degree of extravascular hemolysis. But there may also be a small number of patients who remain transfusion dependent because of (technical difficulty) intravascular hemolysis, which I will go on to talk about.

But have we impacted on this previously quite [worrying] survival? If you look at the next slide again. (technical difficulty) for patients under the eculizumab therapy.

And you can see that it does match very closely with a healthy population. There is a slight separation and this is principally due to the underlying bone marrow failure, which will still need to be addressed concomitantly.

The pink line shows the survival for patients undergoing transplant, just to reiterate again why we don't recommend transplantation purely for the indication of PNH. But patients may require it for the underlying bone marrow failure. Therefore, with this improvement in survival with eculizumab therapy, what else do we aim for for managing patients with PNH in the future?

These are strategies that I would like to see going forward for our patients with PNH. Firstly, if we can have an alternative to intravenous in order to give many of these often young patients, who are trying to work or run a household, to have subcutaneous formulations or oral formulations (technical difficulty) independence. If we could reduce the frequency of administration from every two weeks to less frequent, again, this would free up patients (technical difficulty) travel and be able to supply more work commitment where needed.

The next bullet point about the prevention of breakthrough hemolysis is certainly an important one in our practice. We have seen that there is a significant degree of patients who can have a breakthrough hemolysis on the standard dosing of eculizumab. We actually saw this occurring way back in 2002 when Leeds first undertook the pilot study for eculizumab, and on this slide you can see the eculizumab levels for many patients who were dosed at 900 milligrams every 14 days.

However, this white line shows a particular patient where, on the standard dosing, just immediately before their next infusion is due they have a fall in their trough eculizumab level to below 35 micrograms per milligram and an increase in return of serum hemolytic activity. And, in fact, in

the pilot study where 11 patients were dosed, 2 out of the 11 had a breakthrough hemolysis. So even then we saw approximately 20% of patients not controlled on 900 milligrams every 14 days.

What we don't know, but feel could be one of the reasons is fluctuations in the level of C5. We can see that C5 levels can fluctuate and even be double than other patients, and whether this is one of the reasons we see differences in patient control with eculizumab is something to be explored.

This is data from our center as of September last year, where you can see that in the UK at that point we had treated 245 patients between both the two PNH centers in the UK. But nearly 21% of these patients require a higher dose.

This has not just a significant impact on cost burden for our health system, but is also a risk for patients (technical difficulty) they may have not just a return of symptoms, but a serious risk of complications such as thrombosis. And indeed we have seen such a patient have an inter-abdominal thrombosis during a breakthrough hemolytic event.

At this point I would just briefly like to present one case. This was a patient who didn't live in England, but was someone we eventually got involved with. After having symptoms since 2009, he was eventually diagnosed with PNH in September 2011 with a significant proportion of PNH granulocytes.

He had never required a blood provision, but this previously fit young man would tolerate falls in hemoglobin down to 70 prams per liter. He was commenced with eculizumab therapy in December 2011 and his hemoglobin improved but didn't return to normal. He had continuing lethargy in the afternoons and again, for a young man trying to work full-time, often felt he needed to have a rest in the afternoon.

I met him for the first time in March 2014 when he continued to have lethargy and occasional reddish tinge to his urine. Because he wasn't in England, it took some time for us to get the eculizumab level, which we were doing at that point, and we found that the eculizumab level was low. An application was required to increase the dose of drug.

Before we received -- sorry, we are on slide 33. Before we received the application approval, he was admitted in December 2014 with a clear breakthrough hemolysis with a drop in hemoglobin and an elevation of LDH to more than double the upper limit of normal. He was allowed to be administered an extra dose of eculizumab, but we were still trying to push for an outcome from the application to increase the dose. He was readmitted with further breakthrough and he continued to breakthrough until agreement was given to increase the dose.

This patient is now stable on 1,200 milligrams, two weekly, but as described before, the delay in increase in the dose put him at risk, as we have seen thrombosis occurring in this situation previously. And this is something he was very wary of and certainly had even considered moving to England to see if that would help.

The reason for the delay in approval was obviously the cost burden, and the country in which the application was being processed took their time to justify a significant increase in cost from 900 milligrams to 1,200 milligrams. One theory of why it took a few years for us to see this breakthrough is whether there may be a feedback loop for patients who have higher C5 levels once on eculizumab therapy, and some data alluding to this was presented in June 2016.

Returning back to future strategies, obviously having therapies available to countries all around the world because of an improved cost profile would certainly help many more patients in the world with PNH. And we still need a licensed therapy for patients with PNH who have the C5 mutation, in which eculizumab therapy is not effective.

In summary, I hope I have described how PNH is a complement-mediated disorder, probably one of the pure complement-mediated disorders, but there are two disease processes that need to be concomitantly managed. Eculizumab has shown by proof of principle how complement inhibition therapy can be effective and improve survival, but in order to further improve on the achievements made to date, we would like to look at administration routes and frequency of administration; very importantly, from my point of view, the prevention of breakthrough hemolysis and having correct dosing for patients; looking at cost of therapy; and also having therapy for patients with the C5 mutation.

Thank you very much.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP & GM, ALN-CC5*

Thanks, Anita. That was an excellent overview of a wide-ranging number of topics as it relates to the current state of patients and unmet needs in PNH. We are going to come back to several of these points in a bit. Now we are going to turn, for the next 20 minutes, to Pushkal Garg, who is going to take us through the ALN-CC5 data to date and how we view the program moving forward. Pushkal?

Pushkal Garg - *Alnylam Pharmaceuticals, Inc. - SVP, Clinical Development*

Thanks, Jeff, and thanks, Anita, for the great summary of PNH and the unmet needs that patients still face with that condition.

To start, as a reminder, ALN-CC5 is an investigational GalNAc siRNA conjugate with a subcutaneous route of administration that utilizes Alnylam's enhanced stabilization chemistry, which result in potent and durable inhibition of hepatic C5 production.

We are currently evaluating ALN-CC5 in an ongoing Phase 1/2 study conducted in three parts: Part A and B were single- and multiple-ascending dose evaluations in healthy volunteers, and Part C was an evaluation of ALN-CC5 in PNH patients. I will touch briefly on the single-ascending dose data on the next two slides to highlight a couple of key points about durability and then move to a more detailed review of the data from PNH patients in Part C.

First, a note on safety. In Part A of the study, single doses of 50 milligrams to 900 milligrams of ALN-CC5 were administered to healthy volunteers and were found to be generally well tolerated. There have been no serious adverse events, no study discontinuations, and no clinically-significant laboratory findings reported to date.

Turning to the clinical activity on slide 41, single subcutaneous doses of ALN-CC5 resulted in potent dose-dependent, statistically significant, and highly-durable knockdown of serum C5. Specifically, ALN-CC5 administration resulted in an up to 99% knockdown of serum C5 with a mean maximum knockdown of 98%. Importantly, knockdown was shown to be highly durable, lasting for a period of months.

For example, at the 600 milligram dose, C5 knockdown was still at 97% at day 98 and 94% at day 182. As I will share with you in a few moments, these data support our belief that the durable and [clamp] nature of C5 knockdown could potentially support a once-quarterly, fixed-dose subcutaneous regimen in PNH.

Let me move now to Part C of the study, which was conducted in PNH patients. As shown on slide 42, Part C of the study was designed to assess safety, tolerability, and clinical activity of ALN-CC5 in patients with PNH, including the effects on LDH level. In particular, we explored the potential for ALN-CC5 both as a monotherapy and as an adjunct to eculizumab. This latter category includes the potential for ALN-CC5 to address the needs of patients who have an inadequate response to the C5 antibody.

In addition, as I will share shortly, we also had the opportunity to conduct an exploratory analysis of the potential for ALN-CC5 to lessen the dose and frequency of eculizumab in patients with PNH. A total of six patients with PNH were enrolled in completed dosing: three of these patients had never received eculizumab and, thus, were eculizumab naive, and three patients were currently receiving eculizumab as background therapy. The background eculizumab group included a patient who had an inadequate response to eculizumab, who was being treated with higher-than-labeled doses and was still experiencing breakthrough hemolysis at the time of study entry.

ALN-CC5 was administered at weekly subcutaneous doses of 200 milligrams or 400 milligrams for 2 to 16 weeks. All the initial results I will be reviewing today are based on data transferred up to June 6.

Let's again start with safety. As shown on slide 43, ALN-CC5 was generally well tolerated in PNH patients. There were no serious adverse events or discontinuations due to adverse events. The majority of adverse events, or AEs, observed in the trial were considered mild or moderate in severity.

There was one severe AE of an asystematic transient Grade 3 elevation liver transaminase that was deemed possibly related to study drug. The affected patient was also taking eculizumab, cyclosporine, and anabolic steroids as concomitant medications. Dosing was interrupted in this patient and cyclosporine and anabolic steroids were discontinued and the transaminase values returned to normal.

There were no other clinically significant LFP changes in the study. All other AEs reported were mild or moderate in severity, including mild transient injection site reactions in three of the six patients. There were no clinically significant changes in vital signs, EKG, physical exams, or clinical laboratory results.

Let's move now to the data from the eculizumab-naive patients in the study, which are shown on slide 44.

In these three patients, ALN-CC5 monotherapy achieved robust C5 knockdown in the inhibition of complement activity, as measured by complement classical pathway, or CCP ELISA, and sheep red blood cell hemolysis assays. Specifically, ALN-CC5 resulted in greater than 90% mean/max knockdown of serum C5; a greater than 94% mean/max inhibition of CCP ELISA; and an approximately 75% mean/max inhibition of sheep red blood cell hemolysis. These effects were very similar to those that we reported previously in healthy volunteers enrolled in Parts A and B of the Phase 1/2 study.

I will turn now to the LDH results in the eculizumab-naive patients. Elevated LDH is a marker of ongoing red blood cell hemolysis in PNH. You can see on slide 45 that ALN-CC5 as monotherapy achieved reductions in LDH in two patients with significantly elevated LDH levels at baseline. Specifically in these two patients, we observed LDH reductions of 37% and 50%. However, LDH levels did not go below 1.5 times the upper limit of normal, which is the goal for management of PNH.

In the third patient, who had lower levels of LDH at baseline and received only eight doses of ALN-CC5, we did not see LDH lowering. Since we were able to achieve residual levels of serum C5 less than 1 microgram per milliliter, we have to speculate as to why this is the case. While one possibility is that this is due to extra hepatic sources of C5 synthesis, we believe a more likely explanation is due to the nature of PNH where a functional CD59 deficiency creates a highly-sensitive situation where even minute amounts of C5 can still mediate intravascular hemolysis.

Nevertheless, based on these results, we concluded that ALN-CC5 in the setting of PNH does not have a competitive profile as monotherapy compared with currently approved treatment.

Importantly, in these same eculizumab-naive patients we were able to connect an exploratory analysis to understand the potential for ALN-CC5 to reduce eculizumab dose and frequency. This is shown on slide 46. After ALN-CC5 with dosing was completed, our investigators deemed it appropriate to treat the three eculizumab-naive patients with eculizumab for the management of their ongoing intravascular hemolysis.

Of course, given the multi-month durability of ALN-CC5 mediated knockdown of protein C5, dosing with eculizumab was being initiated in the setting of ongoing serum C5 knockdown. And as a result, the investigators choose to administer a single eculizumab dose of 600 milligrams and monitor the patients' clinical responses via LDH and monitor safety. All three patients achieved rapid lowering of LDH below 1.5 times the upper limit of normal, which was sustained over a full 28-day period.

This is an important finding since the single 600 milligram eculizumab dose over 28 days represents a quarter of the labeled induction regimen of 600 milligrams weekly for four weeks of eculizumab. Accordingly, these results provide preliminary exploratory evidence that knockdown of hepatic C5 synthesis by ALN-CC5 has the potential to reduce the dose and frequency of eculizumab.

Let's now turn to a review of the findings from the three patients who were being treated with background eculizumab at baseline.

As you can see on slide 48, baseline levels of total C5 were almost 4 times higher in this group as compared to the eculizumab-naive patients, suggesting that eculizumab treatment itself may lead to increased total C5 levels. Notwithstanding elevated C5 levels at baseline, ALN-CC5 performed very robustly in terms of knockdown of serum C5. In one patient with nearly 400 micrograms per milliliter of serum C5 at baseline, ALN-CC5 achieved an approximately 98% knockdown of C5 resulting in residual levels of about 8 micrograms per milliliter.

As you can appreciate, the effect of ALN-CC5 on serum C5 levels in this patient was quite robust. Regarding complement essays, both CCP and sheep red blood cell hemolysis levels were below 2% to 3% starting from day 21 onwards. Two of the three patients had normal LDH at baseline and this was maintained during the course of ALN-CC5 treatment.

You will also note that one patient on this slide, patient 0083, showed markedly elevated levels of CCP and sheep red blood cell hemolysis at baseline, and I will now describe this patient in further detail on the next slide.

As shown on slide 49, patient 83 is an inadequate responder to eculizumab. At baseline this patient had an elevated LDH of nearly 1,000 despite receiving an above-labeled dose of eculizumab of 1,200 milligrams every two weeks. In this patient, ALN-CC5 administration resulted in rapid reductions of LDH to below 1.5 times the upper limit of normal and an over 1 gram per deciliter increase in hemoglobin.

Following CC5 administration, the investigator was able to successfully reduce eculizumab to the labeled dose of 900 milligrams every two weeks starting on day 56, and LDH control was maintained out to day 112. We believe this result provides initial evidence of clinical activity for CC5 in inadequate responders to eculizumab, a group that, as Anita highlighted, has been estimated to include approximately 20% to 25% of all PNH patients treated with the C5 antibody.

Finally, we were also interested in exploring if ALN-CC5 mediated inhibition of hepatic C5 synthesis would potentially improve the pharmacokinetics of eculizumab. It's certainly known for many monoclonal antibodies that plasma clearance is accelerated in the presence of antigens.

As shown on slide 50, at baseline, in this same patient receiving 1,200 milligrams of eculizumab, trough and peak eculizumab plasma concentrations were roughly 100 micrograms and 200 micrograms per milliliter. While in the 1,200 milligram eculizumab dose and during the course of ALN-CC5 knockdown of serum C5, there was a marked, over threefold, increase in both peak and trough eculizumab levels.

This elevated exposure to eculizumab was maintained even when the eculizumab dose was lowered to 900 milligrams every two weeks. Thus, these preliminary results suggest that CC5 can potentially improve the pharmacokinetic properties of eculizumab, which further supports the potential for ALN-CC5 to reduce the dose and frequency of eculizumab infusions.

In summary, we are encouraged by these initial results from our Phase 1/2 study, particularly the preliminary evidence observed, which supports reduced eculizumab dose and frequency of administration, as well as data that suggests that clinically-relevant improvement was seen in the patients who had an inadequate response to eculizumab with the addition of ALN-CC5.

We continue to collect data from the patients enrolled in the trial to assess the durability of the clinical effects we've seen in Part C. While our study size was small, we are encouraged by the initial results which indicate that CC5 may enable an entirely new treatment paradigm in PNH that would enable a reduced dose and frequency of anti-C5 monoclonal antibody therapy and could also improve the management of eculizumab inadequate responder patients.

With encouragement from these preliminary data and consistent with our previous guidance, we anticipate initiating a Phase 2 of CC5 treatment in PNH patients in combination with eculizumab in late 2016: the first being a study in inadequate responders to eculizumab and a subsequent study as part of an eculizumab-sparing regimen. To that end, we believe that monthly doses of 600 milligrams and possibly 300 milligrams of eculizumab could be sufficient to maintain LDH at the target level in the setting of quarterly ALN-CC5 administration.

That point is illustrated here on slide 53 where we present the results of PK/PD simulations. You see on the far-left panel the levels of pre-C5 protein and circulation seen with eculizumab when it's administered at the approved maintenance dose of 900 milligrams every two weeks. Note the trough levels of C5 that are achieved -- of free C5 levels that are achieved as well as the between-dose variability indicated by the large peak-to-trough ratio.

The subsequent two panels show the expected free C5 levels when ALN-CC5, given at 600 milligrams once a quarter, is co-administered with lower monthly doses of eculizumab of either 600 milligrams or 300 milligrams. These simulations suggest we should see lower levels of free C5 pathogenic protein as well as less between-dose variability with this novel treatment approach. Thus, these results support the data emerging from Part C,

which suggests that CC5-based regimen may improve the overall disease management, quality of life, and at the same time, reduce the economic burdens associated with intravenous anti-C5 monoclonal antibody therapy with eculizumab.

I will now turn the call back to Jeff, who will speak more about our assessment of unmet need and business opportunity for ALN-CC5 in PNH in the context of this new treatment approach.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP & GM, ALN-CC5*

Great. Thanks, Pushkal; that was excellent. So, what we have now is: we've heard from Anita with an extensive number of patients that they see at the clinics in the UK, moving past that into what Pushkal just reviewed. So we now see some preliminary evidence, clinically and through the PK/PD modeling, to suggest that this new treatment paradigm may be beneficial to patients.

To add to the evidence, what I'd like to share with you now over the next couple of minutes are the results from a market survey that was done back in May to June of this year.

This is a pretty common approach, where there is an outreach to physicians who are treating patients in different diseases. In this case, there was an outreach to physicians in 17 countries, 76 physicians. They self-identify as doctors that treat patients with PNH.

The caveats of research of this nature, of course, are it is self-reported from a physical perspective, number one; and number two, there can tend to be overstatements. So as we go through the figures over the next couple of slides, we interpret them always with the proper caveat that these numbers are not absolute, but directional nature provides some very interesting insights for us.

What types of questions were asked in the survey? You see here a sum up of the questions. We wanted to understand what are the barriers to prescribing today. What are the types of patients they treat; what types of symptoms. What types of patients are not being treated and to try to understand some of the reasons why that this may be the case.

We'd also like to understand the level of satisfaction with today's treatment. Certainly the introduction of eculizumab has helped many patients, but as Anita went through, there are some opportunities for improvement and some new therapeutic options to come in the future should help as well. Then also, of course, we want to try and gauge the level of interest in a new therapy, and in this case, a new treatment paradigm.

Typically, when going through research of this nature, there's an open-ended question at the beginning asking about the level of unmet need. In this particular case, what you are seeing on the slide right now -- and the question is at the bottom: what is the level of unmet need today in support of the need for new complement therapeutics?

And just to orient you to the data, because you will see this on a number of slides sequentially now, the scale goes from 1 to 7 where 1 is not at all supportive in this case and 7 being extremely supportive. Of course, the red line is the average score and then you see in the light blue box, the top 2 box. So really this is the high end of support in this case.

And you see 57% of the physicians -- so this is a report of the percent of respondents in the survey. In this case 57% of physicians said they are very supportive of new complement-based therapeutics, which again reinforces what we heard from Anita and then also what Pushkal began to lead us through.

So then, the next step in the survey would be to introduce a product profile and what you see here is typically blinded in this type of work. In this case Product X is ALN-CC5. And it follows the treatment paradigm that was described in the Part C section from before with Pushkal.

You see pretty traditional elements on the left -- indication, dosing regimen, the route of administration, etc. -- and you see here the target product profile would be the combination treatment of ALN-CC5 and eculizumab in PNH patients. We believe that the dosing at this point in time would be quarterly, which is definitely a difference from today's treatment approach with eculizumab.

And then you see efficacy and safety. It's important that, in this case, the statement of efficacy was comparable to what we see in our Part C of the Phase 1 study. And then also safety as well, maintaining consistent safety with what treating physicians today have in their armamentarium.

Upon seeing this profile, we then turn to a battery of questions and there are two different questions asked on this slide. Starting on the left, the question is: how likely are you to use this new treatment paradigm in your currently-treated eculizumab patients?

And a pretty high number, frankly. You see almost 75% of physicians rated themselves as being extremely likely. That's a pretty high level of interest here in the Top 2 box. Very interesting.

Again, as you move from left to right, what you see on the left are the physician report. Then as you move to the right part of the slide, this is the proportion of patients -- and you see the question down below: if this regimen were available today, in what proportion of their currently-treated patients would they use this combination of ALN-CC5, labeled as Product X, with eculizumab. And 68% also -- even with an overstatement, is a fairly high number. So this begins to provide some insight into the level of unmet need and the level of interest in having new choices be brought to the market.

The next slide then turns to patients who are currently not treated by eculizumab. Some of the reasons of which we get into on the next slide, but essentially it's all the lists you can imagine: some are not clinically severe enough, some have access issues, some have difficulty getting to clinic routinely.

What we are presenting on this slide is simply the level of interest of physicians in treating patients who are not currently being treated today with eculizumab. And you would expect these numbers to be a bit lower because they are untreated patients today, but you still see about 25% of physicians in the Top 2 box, with an average score of 4.4.

By contrast -- that's actually quite good when you look at the level of interest in treating new patients. And that's reinforced by what you see here on the right, which is same sequence of questions: in what proportion of patients not being treated today with eculizumab would you -- in which would you introduce this combination. And you see nearly 40% of patients.

Again, in the currently-treated population you see some very high level of interest, and then in patients who are currently untreated, you see a pretty interesting theme here of a high level of interest in bringing a new choice to the market to help out these patients.

So one of the main questions then comes up is: what are the whys? Why is this unmet need existing today? Why does it exist? What are some of the reasons for levels of satisfaction or lack of satisfaction.

One thing that comes up repeatedly is pricing and access. So you see at the top, in this survey we asked: when patients are not being treated with eculizumab, what are the reasons for it. And as I mentioned before, the first one is lack of clinical severity, which would be expected; not all patients would be treated. But, interestingly, the cost of therapy and/or insurance coverage was the second-highest, most frequent reason given for lack of treatment.

Marrying that with the second point here, where a very, very high number of physicians expressed dissatisfaction with the price of eculizumab, which really is the only modern therapy out there today for patients. Again, it speaks to an opportunity to bring further therapeutics and new paradigms to market to help patients with PNH.

Then, finally, as we begin to pivot from the top half of this slide to the bottom half, even in developed markets -- and just to point to a few examples here. There are barriers in place; not all patients who need therapy can get access to it. Certainly it's not universal, but you see some issues pointed out here.

New Zealand, you see that the government has declined to fund eculizumab in both PNH or aHUS, and this is always in a state of flux. But, again, it's important to look at countries like Australia, for example, where patients with aHUS -- now again, that's not the scope of this conversation, but

it does speak to the access point. Patients who have been then treated and seem to be well need to be reevaluated, and I think that starts to speak to the why. Why is this happening after a patient has responded to a therapy?

Canada limits access in a number of provinces for both PNH and aHUS with eculizumab, and then a recent publication earlier this year coming out of Holland that they are evaluating to stop reimbursement altogether of eculizumab. And that -- again, there are -- the conversation behind this particular half of the slide is a much longer one than we have time for today.

But, again, it does start to speak to there are patients out there who don't have access to the drug or aren't doing well and what do physicians today do with those patients. They are asking for more options. They are asking for some new ideas and we believe that the opportunity that ALN-CC5 presents to them is a very interesting one to help improve the lives of their patient population.

So with that, we have a number of questions that are beginning to line up in the queue. Why don't we turn to the Q&A session?

The first question, Pushkal, I will give to you, okay? Which dosing regimen do you plan to take forward in the Phase 2 studies?

QUESTIONS AND ANSWERS

Pushkal Garg - *Alnylam Pharmaceuticals, Inc. - SVP, Clinical Development*

Interesting. We are still finalizing the thoughts around the design of studies in PNH patients, but those will be coming forward shortly. But I think as we look at the totality of data, I think it's starting to emerge what that dosing regimen might look like.

In Part C of the study, we looked at doses of 200 milligrams to 400 milligrams which were administered weekly to patients, to PNH patients in Part C of that Phase 1/2 study. But when you look at the durability of C5 knockdown that we saw in Part A of the study, reaching out to almost 180 days, and you combine that with the experience that we had in the inadequate responder patients where that combination approach really facilitated a quarterly C5 -- it looks like we can go to a quarterly C5 administration -- ALN-CC5 administration -- perhaps of doses of 200 milligrams to 600 milligrams subcu.

And then co-administered with monthly doses of eculizumab of 600 milligrams, maybe even 300 milligrams. And some of the PK/PD modeling that we've done in simulation really highlights that opportunity. So there really is -- that's what we will be looking at: quarterly CC5 dosing of around 600 milligrams, maybe as low as 200 milligrams, and then eculizumab monthly in the range of 200 milligrams to 600 milligrams -- 300 milligrams to 600 milligrams.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP & GM, ALN-CC5*

Okay, great. That sounds really interesting. It would certainly fit into the type of approach that Anita described before of a new ROA, and I think that's really exciting.

The next question I will take here. What are the cost implications of the eculizumab [sparing] approach if successful?

This is, as we touched on briefly before, a pretty complex issue, but following off what Pushkal said. With a therapeutic like ALN-CC5 being dosed quarterly in a subcu ROA and that enabling a much lower dose of eculizumab, that is a whole, I think, whole different approach to how patients with PNH are being treated. The economics of that are still TBD, but the quality of life improvement for patients we would expect to be pretty substantial.

And, frankly, that's premature to comment a bit now on the cost implications in any specific way, but you can imagine that this type of approach would have not only beneficial effects on drug costs, but also all the other healthcare costs in addition to quality of life of the patients who are going into a clinic now every two weeks for IV infusions.

We have two questions here for Anita. I think the first one that would be interesting to hear your perspective on is: if your clinics in Leeds and King treat 245 PNH patients, can you comment on the number or the percent of patients that you manage that have never been treated with eculizumab?

Anita Hill - *University of Leeds - Honorary Senior Lecturer & Consultant Haematologist, Leeds Teaching Hospitals NHS Trust*

That number that was presented were the number of patients treated with eculizumab. So if I take the Leeds center alone, where I obviously have more up-to-date figures, we are probably at the near 250, 260.

As of now, it's nearly a year after that slide was presented, but we are seeing over 400 patients in total with PNH each year in our center. So, there are obviously over 150 patients not on eculizumab, because at present we don't believe they need eculizumab, and that's why they are under our care for monitoring purposes.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP & GM, ALN-CC5*

Okay. The next question is the -- we touched briefly before in your presentation on the future of PNH therapeutics. After hearing Pushkal's presentation, what are your thoughts on the ALN-CC5/eculizumab concept, this new paradigm that's been proposed and is being evaluated in Part C and then, of course, is being looked at in the Phase 2? What are your thoughts on the potential benefits here and how it might be perceived in your clinic?

Anita Hill - *University of Leeds - Honorary Senior Lecturer & Consultant Haematologist, Leeds Teaching Hospitals NHS Trust*

Yes. So, obviously having had experience now of what could be thought of as the combination paradigm of ALN-CC5 and eculizumab, what you have already alluded to in terms of reduced dosing frequency for the patients, giving them some independence back with their lives, is obviously -- for quality of life -- very good for the patients.

But I think even more importantly than improving quality of life, which is obviously important, is that there should be, I anticipate, a reduction in the breakthrough hemolysis that has caused me most clinical concern over the last decade-plus of managing patients with PNH. The fact that the C-5 level is significantly reduced, allowing a reduced dosing of eculizumab, should mean that if the breakthroughs are due to fluctuations in C5, that this will be prevented.

I would say that at least once a week in our center, knowing the hundreds of patients that we manage, we have at least one breakthrough that we have to be dealing with. And so it is quite a burden to healthcare professionals, as well as a risk to the patient. So I think that would be a significant benefit.

I think the addition of the two drugs that work with different mechanisms of action is certainly very exciting and also quite promising. And we've seen this concept of additional therapies to optimize any disease control with hypertension and diabetes. So, certainly if we find that two complement-targeted drugs, but with different mechanisms of action, can even out a response without fluctuations, the patients will not just see a clinical benefit but also a quality of life benefit.

We've begun to see that from the continuing patients from the Phase 2 and we'll look forward to seeing what happens in onward trials.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP & GM, ALN-CC5*

That's great. That's great news and really good to hear that the patients are well.

The next question, Pushkal, I will give this one to you. What happens during flares and infections? Would ALN-CC5 still be effective in these situations?

Pushkal Garg - *Alnylam Pharmaceuticals, Inc. - SVP, Clinical Development*

Yes, that's interesting. It's important to remember that flares can occur for a variety of reasons in PNH patients and inflammatory states, such as infection, for example, can cause C5 levels to fluctuate. I think Anita highlighted a slide showing some of the variability in C5 levels also that exists. And so I think all those can contribute to flares developing in the context of patients with PNH, untreated and even with -- on treatment with eculizumab.

The treatment paradigm we are exploring using these complementary modes of action -- one, which is preventing C5 synthesis, another which is to mop up the residual C5 that may exist -- may allow us to actually successfully prevent a lot of flares and certainly treat those flares.

It's also important to note that many of the flares that occur in eculizumab are really occurring at the end of the dosing interval, and that's because inadequate levels of eculizumab may occur in some patients. You saw in one of the graphs that we highlighted for that peak-to-trough ratio of eculizumab between -- across the dosing interval.

And so as we've seen in our Phase 1 study, the complementary mechanism of action actually appears to cause ALN-CC5 to have a favorable effect on eculizumab PK and may actually reduce overall those C5 levels and prevent some of that fluctuation of free C5. So, we think -- it's our anticipation, and the early data seem to bear this out, that we will have a favorable effect on flares overall in PNH patients with this novel approach.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP & GM, ALN-CC5*

That's great; that's perfect. So we are getting near the end of the hour. We want to squeeze in a few more questions here, so I will take this one.

From the physician market survey: what is the most frequent reason physicians are not using eculizumab? Well, the first reason that was listed was lack of clinical severity and I think it's important to take that also within the context. And this is something that we've heard in some of the qualitative discussions as well with physicians is the perceptions of clinical severity are still in fact guided a bit by the available therapeutics.

If patients are perceived to be not severe enough to warrant therapy, there's only one therapy out there today. And that is something that we believe that with more choice might enable more patients to be treated.

But, specifically to the most frequent reason; there's a second reason, which is exactly right behind that one, which is access. There was a highly -- frequently reported numbers around lack of insurance coverage or pricing challenges to get access to the drug, which also presents itself as a challenge as, going back Anita's data, as you have to sometimes escalate the dose. This is not only for new patients, but also patients who may be having this breakthrough hemolysis, which is not uncommon.

The next question here, ALXN-1210 aims to establish monthly-dosing regimen and extend the life of eculizumab. How does this affect the attractiveness of ALN-CC5?

Pushkal, maybe a comment from you and then I will close up on that as well with a couple comments about the opportunity.

Pushkal Garg - *Alnylam Pharmaceuticals, Inc. - SVP, Clinical Development*

Sure. The novel thing that we seeing here is that we had this highly potent and durable knockdown of complement C5 and what we believe is actually -- it's wonderful for patients that novel therapies are being developed. Obviously this is not a static field; there's tremendous unmet need and new therapies are being developed.

But, importantly, the same thing that we've seen in terms of complementary mechanism of action with ALN-CC5 versus eculizumab, as well as the favorable effects on pharmacokinetics of the antibody, we believe should apply with 1210 and potentially other C5-lowering therapies. I think

there is a real opportunity for synergy there as well, and so over time as these other therapies mature, we will be looking at those types of approaches as well.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP & GM, ALN-CC5*

Absolutely agree from a commercial business perspective as well. I think the addition of a new therapeutic, like 1210, to the market is good for patients. ALN-CC5 is good for patients and we think that with this treatment paradigm, ALN-CC5 as a foundational therapy, will enable extended-dosing intervals of any monoclonal antibody. I think that's really where we see the opportunity for patients and the opportunity for the healthcare systems as well.

Good; one more. Pushkal, I will ask you to start with this one and then maybe I will add a comment on the back end.

Why do you think you will be successful in other complement-mediated diseases? Assuming you move forward with other development plans, which we have talked about.

Pushkal Garg - *Alnylam Pharmaceuticals, Inc. - SVP, Clinical Development*

I think, as you are highlighting -- the questioner is highlighting, beyond PNH eculizumab has shown activity and has been approved in atypical HUS and there's recent emerging data suggesting clinical benefit potentially in myasthenia gravis. And so the obvious question is: can we pursue ALN-CC5 in those fields, particularly given the data that we are seeing in PNH in terms of the lack of fully-robust activity as monotherapy, but a better use in combination?

I think a couple things I would highlight is certainly both what the eculizumab data support, I think -- our proof of concept that complement plays an important role in the pathogenesis of those diseases and reducing complement activity can be important.

I think I would point out that not all complemented-mediated diseases are the same. Anita highlighted this very well that there's a particular defect in PNH that makes these red blood cells extremely vulnerable to even minute amounts of circulating C5. And so you really need -- and our data I think are supporting that -- real complete inhibition of C5 to effectively manage LDH in disease symptoms.

I think, in contrast, there are data emerging, small-clinical [K series] in aHUS, some preclinical data that we will be presenting at AANEM later this year in myasthenia gravis that suggests that the levels of complement inhibition we are seeing -- over 95% inhibition of C5 synthesis -- may be sufficient to actually treat as monotherapy in atypical HUS and in myasthenia gravis. And so these are areas we are exploring. We are talking to experts and we will be thinking further about development in one or more of these indications potentially next year.

Jeff Miller - *Alnylam Pharmaceuticals, Inc. - VP & GM, ALN-CC5*

Perfect. Thanks, Pushkal. First of all, Pushkal, thanks to you. Anita, thank you so much for taking the time to share your thoughts with us.

Christine, I will turn it back over to you to wrap up.

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

Perfect. Thank you, Jeff. This concludes our RNAi Roundtable for today. Replay and slides will be posted on the Alnylam website later today at www.alnylam.com/roundtables with the transcript to follow shortly thereafter. You can also visit the page to view bios of today's event speakers.

We look forward to your participation on Tuesday, September 13 at 11:30 AM Eastern Standard Time as we discuss our ALN-AS1 program in development for the treatment of acute hepatic porphyrias and in the weeks to follow to discuss additional programs from Alnylam's pipeline of investigational RNAi therapeutics. For more details, please visit alnylam.com/roundtables.

Thank you, everyone and have a great day.

Operator

Ladies and gentlemen, thank you for participating in today's conference. This does conclude the program and you may all disconnect. Have a great day, everyone.
