Alnylam Pharmaceuticals Inc (ALNY)

Alnylam Pharmaceuticals Inc RNAi Roundtable: ALN-HBV for the treatment of hepatitis B virus (HBV) infection

11-Oct-16 Conference Transcript

Alnylam Pharmaceuticals Inc RNAi Roundtable: ALN-*HBV* for the treatment of hepatitis B virus (*HBV*) infection

Cambridge Oct 11, 2016 (Thomson StreetEvents) -- Edited Transcript of Alnylam Pharmaceuticals Inc conference call or presentation Tuesday, October 11, 2016 at 1:00:00pm GMT

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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 Josh Brodsky for opening remarks. Josh, you may proceed.

Josh Brodsky, Alnylam Pharmaceuticals, Inc. - Associate Director, IR & Corporate Communications

Good morning, everyone. Thanks for joining us for today's RNAi Roundtable to discuss our progress with ALN-HBV, ***in*** development for the treatment of chronic hepatitis B virus infection. I'm Josh Brodsky, Associate Director of Investor Relations and Corporate Communications at Alnylam.

With me today are Pushkal Garg, Senior Vice President of Clinical Development at Alnylam; Heiner Wedemeyer, Managing Senior Physician and Assistant Professor at Hannover Medical School; and Laura Sepp-Lorenzino, Vice President, Entrepreneur-in-Residence at Alnylam.

Before I turn the call over to Pushkal, I just want to make a few comments. Today's RNAi Roundtable focused on ALN-HBV ***is*** the last one in a series of roundtables that we have been hosting this summer and early fall. Today's event will end at around 10:00 AM Eastern Time. Pushkal will moderate a Q&A session at the conclusion of the presentations and if you would like to submit a question, you can do so at any time during the event by clicking the Ask a Question button located above the slide window on the webcast player.

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

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

Thanks, Josh, and thanks, everyone, for joining us today to hear about our ALN-***HB***V program.

As all of you know, Alnylam is the industry leader in RNAi therapeutics, which represents a whole new class of innovative medicines. RNAi is a powerful approach for gene silencing that harnesses a natural and catalytic mechanism, and through Alnylam's efforts, RNAi is a clinically-proven approach.

As you'll see on slide 7, Alnylam has developed a pipeline of products focused in three strategic therapeutic areas, or STArs. These are genetic medicines, cardio-metabolic diseases, and hepatic infectious diseases, representing a range of disease opportunities from rare to common to global.

On slide 8 you can see each of the specific programs listed by STAr, showing the eight products that we have currently in clinical development. Today we will focus on ALN-***HBV*** within our hepatic infectious disease STAr, as highlighted on slide 9.

Slide 10 shows you the agenda for today's RNAi Roundtable. We will begin with Laura Sepp-Lorenzino, who will provide an overview of the ALN-***HBV*** program. After she concludes, Dr. Wedemeyer from Hannover Medical School will provide an overview of chronic hepatitis D virus infection. Following Dr. Wedemeyer's presentation, we will begin the Q&A session so please remember to submit your questions as we go.

And with that I will hand it over to Laura. Laura?

Laura Sepp-Lorenzino, Alnylam Pharmaceuticals, Inc. - VP, Entrepreneur-in-Residence

Thank you, Pushkal. Good morning, everybody, and thank you for joining our RNAi Roundtable.

As shown on slide 11, hepatitis B infection is the most common serious liver infection in the world. Worldwide there is 2 billion people, that is one in three people, who have been infected with ***HBV*** and there are approximately 290 million people that have chronic diseases. And although prophylactic vaccines have been available for over two decades, there's still 10 million to 13 million new infections per year with most patients being unaware of the infection and many, many patients being untreated.

Chronic infection results in fibrosis, cirrhosis, and is the leading cause in the development of hepatocellular carcinoma, or HCC, and results in about 1 million deaths annually.

There are two approved classes of drugs for chronic ***HB***V, one are the oral nucleotide inhibitors of the viral polymerase, often known as nukes. These are given chronically. The second class is the pegelated interferon, which is given as an injectable weekly for 48 weeks.

These two classes of drugs are efficacious in reducing viremia, decreasing inflammation, decreasing fibrosis. They reduce the risk of development of HCC, but they do not eliminate it. And, importantly, neither class results in significant cure rates. And by cure, we are talking about the absence of viral products in blood and a reflection of control, immunological control of the viral infection.

It is clear that patients need new options, patients that are facing lifelong therapy in this group of nukes. Interferons have poor tolerability; new antiviral therapies are needed.

So by silencing all viral products, as we will discuss in the following slides, ALN-***HB***V is expected to elicit a combination of antiviral mechanisms that will lead to increased viral suppression within the hepatocytes and reactivation of an effective immune response that will lead to control of the viral infection, also known as functional cure.

If we go to slide number 12, for ALN-***HB***V we apply the same framework that we use for all the other programs in the Alnylam pipeline. It starts with a genetically-validated, liver-expressed target gene; and liver because the liver is where our delivery solutions function most efficiently. In the case of ALN-***HBV***, the HPV virus, which is the direct disease-causing agent, is the target.

The second part of the framework is the incorporation of biomarkers in Phase 1 to evaluate the drug candidate pharmacodynamic performance and to understand the dose level and the dose regimen that can be applied in subsequent Phase 2 and 3 trials.

The last aspect of the framework is the incorporation of well-defined endpoints for approval. For ***HBV***, we would be looking to elicit a sustained virological response after discontinuation of all therapies. So not only of ALN-***HBV***, but any other therapies such as nucleoside analogues, and these would be following a finite course of treatment.

Slide number 13 shows -- begins to show more data on the candidate and this is data that we had shared before. We have chosen an siRNA target site that is highly conserved across all viral genotypes. It has a 97% perfect homology, which, if we allow one mismatch, that homology across genotypes A to J rises virtually to 100%.

The siRNA target site is located in the X open review frame. That is a region that is present in all viral transcripts, which in the graphic on the top are depicted as blue lines.

Based on bioinformatics and limited expression analyses of RNA, we expect that this target site will not only lead to silencing of the viral genome expressed transcripts, but also transcripts that are expressed from integrated viral genome into the host DNA. By being present in all the transcripts, a single siRNA will be capable of silencing all the RNAs. These are the long RNAs that code for the pre-genomic RNA, the transcript that serves as the template for viral replication, as well as the RNAs that code for the core protein, the E antigen, the polymerase; and those that are coded by smaller transcripts coding for the small, medium, and large S antigen and the X protein.

By silencing all these viral products at once, we are de facto eliciting a combination of antiviral mechanisms, similarly of what would be achieved if we were to combine a nucleoside analog to inhibit a polymerase, a core inhibitor, a secretion inhibitor, and the future X protein targeting therapies.

If we go to slide number 14, on the top there is a depiction of the conjugate structure. So the siRNA that was selected to target this target site in the X open review frame was modified applying our enhanced stabilization chemistry and it was conjugated from the three [prime] end of the sense strand or the passenger strand to a [tri] N-acetylgalactosamine sugar. As we have shown with other candidates, this tri GalNAc mechanism of delivery is very effective for targeting siRNAs to hepatocytes after a subcu administration.

But shown on the bottom left is a study done in a surrogate mouse model of ***HB***V infection using the adenoviral vector expressed ***HB***V genome and measuring the levels of S antigen reduction in the serum of the mice after a single subcu injection. As you can see, there is a dose-dependent, profound, and durable silencing of S antigen.

We have seen that the single subcu dose achieves over 2 logs and that reduction could last over a month to two. In studies not shown here that were presented before, we have shown that multiple dosing can further extend duration.

On the right, there are two images. These are immunohistochemistry of S antigen expression in the liver of these AAV-***HBV*** mice. And as you could see, a single dose of 3 milligrams per kilogram of ALN-***HBV*** can lead to significant suppression of S antigen protein levels.

In slide number 15, we are showing the target product profile for ALN-***HB***V. Again, by suppressing the production of all viral products, we are going to be eliciting a combination of antiviral mechanisms. And by suppressing the production of tolerogenic ***HBV*** antigens, we will be promoting the emergence of an effective host immunity against the virus, which in turn would lead to a long-term functional cure.

We are looking to have a six-dose monthly 100 to 200 milligrams, a course of treatment that would be 12 to 24 months, after which we would be looking to have sustained biological response after cessation of all therapies. For safety, obviously we're looking to have a well-tolerated drug, including in combination with other therapies existing and in development for HBV ***inf***ection, including immunomodulatory therapy.

Slide number 16 depicts the ongoing Phase 1/2 study for ALN-***HB***V. As with all Phase 1 studies, the primary objective is safety and tolerability. The secondary objective is pharmacokinetics of the drug and antiviral activity, looking at the production of viral antigens: in blood S antigen and E antigen for E antigen positive patients. And planned, but not shown here, would be effects on ***HBV*** DNA.

The study has three parts. Part A is a single ascending-dose study in healthy volunteers. The dose starts at 0.1 milligrams per kilogram, 0.3, 1, 3, and would have two optional cohorts. Part A of this study was initiated in July 2016 in the UK.

This will be followed by a Part B, a single ascending dose in chronic ***HB***V patients who are stably suppressed with nucleoside analogues for over 12 months. Again, the doses are similar, 0.1, 0.3, 1, 3 and we have three optional cohorts. This will be followed by Part C, multiple ascending dose in patients, also stably suppressed on nucleoside therapy for over 12 months. Here we would be looking at four monthly doses.

So slide 17 gives a snapshot of the competitive landscape for ***HB***V. And before I go into more detail, I want to highlight a mistake on the slide for ARC-521: the text on the first row it should be on the next row for Arbutus-1467. That mistake will be corrected in the slide that will be downloadable from our website.

So for ALN-***HB***V we are looking at a subcu injection, no need for premedication, well-behaved drug as proven by other pipeline candidates for multiple therapeutic indications and target in the liver. We understand the performance of these drug candidates, the dose response, the duration, and this is what we are expecting to see for ALN-***HBV***.

The other programs are more advanced. We have ARC-520 and ARC-521. Both use two cholesterol siRNAs that are given by IV infusion in combination with an agent that is required for endosomal release of the siRNA and activity of the siRNA liver; that is the GalNAc mellitin-like peptide. These are given by IV infusion with oral antihistamine premedication. So far only data for ARC-520 has been released and has shown low activity, low efficacy in E antigen positive patients with very poor efficacy in E antigen negative.

The Arrowhead team has done very elegant studies in chimps showing the contribution of S antigen from integrated DNA as a possible interpretation for the lack of efficacy of the candidate in the E antigen negative patients. For that they have developed ARC-521 as a follow-on therapy in which in addition of targeting an siRNA to the X open reading frame, they have a second siRNA targeting the S antigen from both sources, the integrated DNA, as well as the viral genome.

Arbutus has two candidates: 1467 is in the clinic, a follow-on is 1740. In this case it is a lipid, not a particle formulation, that is given by IV infusion and requires pretreatment with steroids. And know that steroid pretreatment is contraindicated in chronic ***HBV***.

The emerging data for Arbutus 1467 also shows significant underperformance with 0.1 to 0.6 log decline of S antigen in -- sorry in E antigen negative patients. The next candidate will be the Ionis GalNAc-targeted anti-sense, which is given by subcu injection. It leverages the Alnylam GalNAc technology for delivery and is currently in Phase 2 and no data has been released yet.

But, again, going back to ALN-***HB***V, we are expecting that it will be well behaved; that the siRNA will be able to target both S antigen from the -- not only the DNA genome of the virus, but also the integrated fragments. And, importantly, there is no need for premedication.

Going to slide 18, as we think of the performance of ALN-***HB***V, we are also thinking of additional indications that will be appropriate for our drug candidate. And we are using this opportunity today to introduce the concept of targeting ALN-***HBV*** in chronic hepatitis D virus infection.

Professor Wedemeyer is going to go into more detail about the disease and the opportunity, but just as a quick intro, the chronic -- the HDV virus is an RNA sub-virus that depends on pre-existing or co-infection with ***HB***V in order for the virus to propagate. There is about 5%, 5% to 10% of patients who have chronic ***HBV*** infection are co-infected or super infected with HDV. There's a total of about 15 million to 20 million patients infected worldwide with about 80,000 patients in the US.

It is a very severe infection and there are no current curative therapies available. Peginterferon has some small response, but it's not durable, and there is a tremendous need for new therapies. So as we think of ALN-***HBV*** and its ability to suppress this antigen from both sources, the integrated DNA and the CCC DNA, we are looking at two potential outcomes in HDV.

One would be HDV suppression, where patients will receive chronic, ongoing therapy for reduction of S antigen; thereby, directly suppressing HDV replication and HDV viremia. The next is that if we are able to induce an immune control of the ***HBV*** infection,

then that by itself will result in a chronic HDV cure.

So to wrap up my part of the presentation, we are excited of thinking about ALN-***HB***V, not only to elicit functional cures for chronic hepatitis B, but also for chronic hepatitis Delta. I made all these points during my talk.

Again, I want to highlight that with this mechanism, this drug format we are looking at low volume, infrequent, subcu dosing; no need for premedication. We are thinking that this will lead to improved compliance due to convenience of this infrequent dosing, good tolerability, and we're expecting that we will be able to reach across the different chronic HBV ***pat***ient segments including young immune tolerant and patients that today are outside the treatment guidelines.

Another point is that, for our drugs, they are stable at room temperature and as we are thinking of chronic ***HB***V being a global problem, particularly in Asia and Africa, not having a cold chain it really simplifies global distribution and accessing the patients in need. So with that I will pass it on to Pushkal.

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

Thank you, Laura. And thank you for giving us a great overview of the ALN-***HBV*** program, the pharmacology, the nonclinical data and framing out this interesting opportunity in hepatitis D.

We are very fortunate today to have Professor Heiner Wedemeyer here with us, who is a managing senior physician and assistant professor in the Department of Gastroenterology, Hepatology, and Endocrinology at Hannover Medical School. Dr. Wedemeyer is an expert in hepatitis D virus and he has agreed to talk to us and give us -- educate us all about the unmet need and biology of this infection and where ALN-***HBV*** may play a role.

Dr. Wedemeyer?

Heiner Wedemeyer, Hannover Medical School - Managing Senior Physician & Assistant Professor, Department of Gastroenterology, Hepatology, and Endocrinology

Thank you very much, Pushkal, for the kind introduction. And, indeed, I always like to speak about hepatitis Delta, which is a largely underestimated liver disease worldwide. Not only in, let's say, developing countries, but in particular also in Western countries and also North America, the importance of hepatitis Delta and severity has, in my view, not been appreciated enough over the last years.

What I thought is briefly to introduce to you the disease and also the current treatment landscape and very briefly then to give some ideas how to -- what could be passed to new therapies for hepatitis Delta.

On slide 22, I have to highlight my disclosures, which is obviously important. This includes also connections to companies developing drugs not only for hepatitis B, but also specifically for hepatitis Delta.

On slide 23 you can see another picture of the scheme of the hepatitis Delta virus. Laura mentioned already that this is a quite unique virus. It is an RNA virus that hijacks hepatitis B.

It is the smallest of all known animal viruses. It has a very particular structure with RNA. Importantly, the virus itself, the genome, does not encode for own viral enzymes. Meaning it is not possible to develop, let's say, polymerize inhibitors or protease inhibitors against HDV because HDV uses host enzymes for replication.

It does only encode for one single antigen with some post-translation and modification steps so that in the end in the cell there are two antigens, the small and the large HD antigen, but encodes only one antigen. And then basically around this HDV RNA with the antigen, you have the surface antigen of the hepatitis B virus. This is basically -- therefore, you have the identical modes of transmission; it's a co-infection of hepatitis B virus.

We are understanding now in more detail the biology, the importance of the different HDV antigens, but again I have to highlight here that we have yet no direct mechanisms to target virus-specific products.

So if this is a co-infection, then obviously, as shown on slide 24, you have either simultaneous co-infection or you have patients who carry already the hepatitis B virus and have become super infected with HDV. In case of acute co-infection, this usually leads to very severe acute disease; more frequent fulminant disease, frequently with fatal outcomes, but this fortunately has become a rather rare event. What is more common is the super infection, so you have patients carrying ***HBV*** who become super infected with HDV and then these patients develop chronic disease in 90% of the cases, which also is more severe.

The prevalence worldwide, shown on slide 25, and there you can see a quite heterogeneous picture. You have countries with low HDV prevalence and then you have distinct hotspots. For example, in the Amazonian area in western Brazil they have some villages with extremely high Delta prevalence.

You also have countries like Mongolia. In Mongolia, there are more patients dying from HDV than from cardiovascular disease. So it's extremely prevalent there.

And also in Europe we have some countries with high prevalence. For example, in Romania up to 20% of the hepatitis B patients are co-infected with HDV.

The other point is that we have, like for other viruses, also different genotypes. The most frequent genotype in the Western world is genotype 1 infection, while you have other genotypes in Africa and South America and also in Eastern Asia. But for us genotype 1 is the challenge and the biggest problem.

On slide 25, this is just one example showing -- or 26 -- that it's also prevalent in HIV-infected persons. It has been shown that this is associated with morbidity and mortality. So if Delta is -- you can find it frequently worldwide, then the next question is, well, why has it been underestimated? The biggest challenge is for us doctors to educate the colleagues that they simply test for Delta.

Just one example on slide 27, that in the US less than 10% of HBS antigen positive patients have actually been tested for anti-HDV. And as I give my educational talks to general practitioners, to gastroenterologists, usually my first slide for Delta is remember only one thing from this talk: Test your B patients for Delta. And this is the most important factor at this stage.

Just one example on slide 28 that Delta is really taking a severe course. This is data from Greece, where they compared the outcome of co-infected patients, D/B co-infected, versus B mono-infected patients. Really showing the severity of the disease that after only five years or six years of infection, more than one-third of the Delta patients had already developed complications of liver disease. And there's other data from different countries really confirming the severity of this chronic viral infection.

On slide 29, this is kind of historical view where we have seen, let's say, an evolution of clinical presentation of patients. While in the 1980s and 1990s we have seen young patients, frequently IV drug users, we now see older patients, immigrant populations which have severe disease. And on the left side of the slide you can see some references confirming the severity of Delta with cohorts from Italy, from Spain, from Germany, and also from other countries.

Briefly on slide 30, it is shown that the ***HB***V genotype matters. Very unfortunately the genotype we are talking about in Western Europe and in North America, HDV genotype 1, shows a more severe cause of liver disease than, for example, genotype 2, which can be found in Eastern Asia. And most likely the most severe genotype is genotype 3 infection.

There is one paper shown on slide 31 from South America really showing that rather young patients -- you can see in the third row that there are many patients below the age of 25 who have already developed advanced liver fibrosis which is really remarkable. You do not see this in hepatitis C mono-infection and hepatitis B mono-infection, but you can see patients at an age of 20, 25 years who have developed liver cirrohosis in case of hepatitis Delta.

So then the next question then obviously on slide 32 is, if this can be really a severe disease, does it take a severe course in every patient? How can we, from the clinical perspective, identify patients with a higher risk for disease progression and then obviously also with a higher need for novel antiviral treatment approaches?

We can look for simple biomarkers. For example, on slide 33 this is a paper from our group showing that you can look for anti-HDV IgM antibodies, which you can also find in chronic disease. And if these antibodies are absent, then you usually have a milder course of disease. While if these antibodies are present, then these patients have a higher risk for disease progression.

And on slide 34 we are showing a clinical score which we developed here in Hanover where we could distinguish three groups of patients with an intermediate course, a benign course, and a severe course of liver disease. This is a clinical score which we use in our practice to identify patients which, for example, should receive interferon treatment, which I will mention in one minute. And on slide 35, you can see that this score doesn't only work in my court here in Hanover, but also in Barcelona and Dusseldorf.

Okay, so what can we do now? Treatment of hepatitis Delta, slide 36; I showed you this disease is not infrequent. I showed you that the disease is severe. What can we do?

As I mentioned before -- this is the slide I showed in the beginning on slide 37 already -- there are no HDV-specific viral enzymes. So no HDV protease, no HDV polymerase, which is obviously a challenge. We have in principle then the option of targeting something common to ***HBV*** and HDV: so ***HBV*** entry, targeting the mother virus, ***HBV***, or some, let's say, post-translational specific steps to HDV, which is a little more challenging.

And as the drugs we have for ***HB***V do not target directly ***HB***V, obviously the ***HB***V polymerase inhibitors do not work. Therefore, we are left with interferon, so the other concept that Laura introduced to you also for HDV infection. This is shown on slide 38. This was the landmark paper that we performed with German centers together with centers in Greece and Turkey where we used interferon -- peginterferon alfa-2a, either alone or in combination with a polymerase inhibitor against ***HBV***, which was at that time adefovir.

The message of that slide is basically that, yes, interferon works against HDV, but only in, let's say, one-quarter to mostly one-third of the patients. And also that, as to be expected, the combination therapy was of similar efficacy as compared to the interferon monotherapy, where there was no effect of the polymerase inhibitor against ***HBV*** alone.

So this was the main message of that paper and what we found at that stage is that there may have been a synergistic effect of both drugs against the mother virus, or ***HB***V, in terms of HBS antigen suppression, which was an interesting note. But adefovir today is no longer used because adefovir is associated with renal toxicity and, therefore, it basically is no longer recommended by guidelines. And as adefovir is no longer recommended, the question now what about combining interferon with tenofovir, the current standard of care for hepatitis B. We also performed a trial investigator-initiated and on slide 41 you can see the design.

So we did investigate interferon plus tenofovir and then we used this regimen not only for one year but also for two years. 96 weeks we tortured our patients with interferon. I can tell you this was in clinical practice not fun at that stage, but we did it. We completed the trial and on slide 42 you can see the results.

It's a busy slide. The message for you is the unfortunate thing is that even by extending treatment duration to 96 weeks, we could not increase overall response rates and this is shown. So 24 weeks after the end of therapy only around one-quarter of patients were still HDV RNA negative. We still had post-treatment relapses and this was very unfortunate. So personalizing treatment duration did not really help to the patients.

And on slide 43 we also looked for the HPS antigen. The slide before was HDV RNA; now we're looking to the hepatitis B surface antigen and so the effect on HBV. And there was no longer any synergistic effect between tenofovir and interferon, so it did not make a difference whether we used interferon alone or in combination with tenofovir. Meaning that there is, at this stage, no role of combination therapy for hepatitis Delta.

And then we had a further challenge and this is introduced on slide 44 and then slide 45. So what is happening if you follow our patients after interferon therapy further? Some of you may follow the HCV field and there we are used to the endpoint sustained virological response. Meaning, if I am negative 12 or 24 weeks after the end of therapy, this is almost equivalent to viral elimination from the body, so this is really cure.

For Delta, this is not the case. Some people make jokes about me because I published in the New England Journal of Medicine that I cured 25% of HDV RNA positive patients and three years later we published in Hepatology we were actually wrong. That we disproved our New England Journal of Medicine paper because those patients who were negative 24 weeks after the end of therapy -- and this is shown on the right side of slide 45 -- that many patients relapsed thereafter. So interferon can suppress HDV in some patients, but it does not induce long-term cure.

For clinical development, it's still important does this treatment have clinical effects? FDA and EMA, they will not only ask for my surrogates HDV RNA suppression also, but they obviously want to approve a drug only if there is a clinical long-term effect. And this has been questioned by the agencies and by many colleagues in the field whether the patient benefits if I suppress HDV RNA and maybe even if I lose S antigen.

There's very old data by Patricia Farci shown on slide 47, where she looked 10 years after interferon therapy and could see if patients received high doses of interferon that then the survival of patients was better. But this was, let's say, interferon used in the early 1990s, old interferons; three times weekly injections.

We just published in Hepatology -- the paper is in press, not yet online; should go online next week or so -- that interferon-treated patients or peginterferon treated patients really benefit if they respond to therapy and that they have a better outcome than patients who have not been treated with interferon or received nukes ***HB***V alone. This is shown on slide 48.

And very importantly, on slide 49, which may be then relevant for the new ideas to get rid of HBs antigen from the body. For example, right now our approach is to reduce S antigen, and even maybe to eliminate HBs antigen, is this a good thing for the patient? You can clearly see here that those patients, very few patients who lost HBs antigen in our cohort here in Hanover, they had a much better outcome than patients who remained HBs antigen positive. Suggesting that this is a very hard endpoint, which hopefully then also -- not hopefully; which should be accepted also by agencies.

On slide 50 then this is a summary of the management of hepatitis Delta. From a clinical perspective, I can distinguish patients with mild disease but also very severe disease, so those guys who require immediate treatment. We have only interferon as the only effective treatment options. However, long-term follow-up is required and I showed you that there is no cure for hepatitis Delta.

And the problem is also that only one-quarter of patients in the end benefit from interferon treatment. And the other problem is that it's not only that only one-quarter of patients respond to interferon, the problem is that mostly half of the patients can't actually be treated with interferon, because the majority of patients has either too advanced disease or has contraindications for interferon.

So the long-term benefit of interferon treatment for Delta is in the end only less than 10% of patients have a long-term benefit of interferon therapy. Therefore, we have a high urgent need for novel therapies against Delta.

Maybe we can switch slide 51 and 52 and directly move to slide 54, where we can have another sketch of the lifecycle of HDV, which are the possible ideas to treat hepatitis Delta. One obviously is to block the entry of the viruses, both B and D.

There is data; there is the entry inhibitor myrcludex developed by Stephan Urban and first proof-of-concept trial in very few patients, 14 patients, has recently been published in the Journal of Hepatology in September, showing that myrcludex is able to block ***HB***V and HDV entry and this may have an effect on HDV levels. But there are more trials needed really to identify those patients who really benefit.

On slide 56, there is illustrated that there may be another specific step of the HDV lifecycle which could be used as an antiviral target. This is the so-called prenylation inhibition, so this is a distinct step which blocks virion assembly and packing of viral particles by blocking the farnesyltransferase. And indeed, here we have also the first proof-of-concept data being published and this is shown on slide 57.

Last year at the NIH trial on the prenylation inhibitor lonafarnib, which showed a dose-dependent reduction of HDV viral load in these patients. These patients received treatment for four weeks at ASLD; this year in Boston there will be more data where I, for example, will present a dose escalation study on this compound. But the compound also has side effects, GI toxicity, and we have to see how the clinical importance will be then in the long term.

The last option for treatment of Delta would be then to block sub viral particle formation. There is also small proof-of-concept trials which have been initiated. Also here we are lacking yet fully-published data, but this is another theoretical idea for a new treatment

in hepatitis Delta.

So to summary on slide 59, as I mentioned interferon remains the only treatment option. We have ***HBV*** entry inhibition, prenylation inhibition, and block of particle formation as potential new ideas which are currently explored in clinical trials.

But the most important message is obviously in terms of or considering the severity of the liver disease, we need really novel strategies to achieve HBs antigen clearance because, obviously, cure of ***HB***V will also be cure of ***HB***V/HDV infections. And one may -- from the clinical perspective people may question do we really need new therapies for hepatitis B if we have already the good nukes? I can tell you we definitely need new therapies for hepatitis Delta. It's an unmet need and many of these new strategies should urgently be explored also against hepatitis Delta.

Finally, on slide 60 I want to highlight that we have initiated an international hepatitis Delta network, which is a large database of more than 1,000 patients, which should allow us also to validate surrogates for the long-term outcome and also to identify patients being treated in different regions of the world.

So this was my introduction to Delta and I turn it back now to Pushkal. Thank you.

QUESTIONS AND ANSWERS

Answer – Pushkal Garg: Thank you, Dr. Wedemeyer. That was really elucidating and very helpful overview of hepatitis Delta and the biology and emerging therapies.

At this point, we're going to open it up for question-and-answer for both of our speakers. As a reminder, please submit your questions by clicking the Ask a Question button located above the slide window on the webcast player.

We'll give a moment for questions to come in. We've started to get some coming in, so maybe -- the first one, Laura, is for you which is you've talked about the Phase 1/2 study that's ongoing. What are the plans now in terms of when efficacy and/or safety data will be reported out from that study? And can you comment on the status at all?

Answer – Laura Sepp-Lorenzino: The Part A of the study started in July of this year. We are doing Part A in the UK and Parts B and C are being done in the UK and six Asian countries. We -- as we had announced before, we expect to provide an update mid 2017, so at this stage there is nothing to report.

Answer – Pushkal Garg: Great, great. The other question that came in for you, Laura, was you had spoken a bit about single agent versus combination. So can you talk a little bit about how you are thinking about whether ALN-***HBV*** will be positioned and how it's going to be studied and what potential therapies might it be combined with going forward? What's the range of options and how will you understand that?

Answer – Laura Sepp-Lorenzino: That's an important question. In our Phase 1 trial it's already designed as a combination therapy, so we are looking at patients who are stably suppressed by nucleoside analogues tenofovir and entecavir. So their DNA replication should be or viremia should be controlled.

However, as we know, nucleoside analogues do not significantly impact S antigens as a reflection of continued transcription happening in the hepatocytes. The first combination that we are doing is already in Parts B and C with nucleoside analogues. And although we don't expect to see any declines in DNA because it's not detectable, we do expect to see inhibition, knockdown of S antigen, and E antigen in the E antigen positive patients.

For the Phase 2, we are going to be expanding the number of combinations. One obviously is the combination of nukes with ALN-***HBV*** succession to lead to functional cure in a percentage of patients. But then what other therapies?

In the US pegylated interferon is not commonly used; however, we are considering that combination ex-US. And then as new mechanisms are being developed, like core inhibitors for example, this is of interest for us to evaluate investigational drugs. And it's important as we think of the strategy of taking two investigational drugs into short [bio market range] Phase 2 studies.

Last, but obviously very importantly, is also any immunomodulatory therapies, not only --. So there is some work on (inaudible), but we have seen presented by, for example, Dr. Ulrike Protzer very interesting preclinical data in which animals were treated with a short hairpin RNA to reduce expression of all viral transcripts, similarly to what we are doing with ALN-***HBV***. And followed by a therapeutic vaccine.

In this sequential therapy there was a significant increase in T cells specific for ***HB***V. So that leads into a potential combination therapy in which patients will be first treated with ALN-***HBV*** and then followed up with a therapeutic vaccine. And that may be, obviously, very important in those patients in which immune suppression is almost or completely suppressed.

So if there is no T-cell function to be reactivated, we may need to generate new T cells, which in the absence of antigens may lead to a sustained virological control -- immunological control of infection.

Answer – Pushkal Garg: Great. Thank you, Laura. Professor Wedemeyer, a question for you. The question is just around is the incidence and/or prevalence of HDV growing and why? Is it a matter just of diagnosis or what's happening in terms of the overall epidemiology of the disease? Is the incidence actually of new infection growing?

Answer – Heiner Wedemeyer: This is different from country to country. In Western countries let's say the number of patients we see in the clinic is increasing, but this, in my view, reflects a better diagnostic frequency. That physicians are following our guidelines.

While there are some countries, like in Mongolia, where it really looks like the incidence is still increasing. There's still patient-patient transmission. In other countries, like in Italy, there has been a significant decline over the last 10, 15, 20 years with concurrent preventive measures also to prevent ***HBV*** infection.

So, overall, it's diverse, but I think it's -- for us it's not really the question whether the disease is increasing yes or no. I think we first have to do our homework and simply to diagnose those patients who are walking around there. And once we have done that job I think we have identified so many patients which require urgent treatment, so this should be the priority of our public-health efforts for Delta.

Answer – Pushkal Garg: That's great. Maybe a follow-up question that came in for you, Dr. Wedemeyer; was talking about the unmet need. You've certainly highlighted the criticality of this disease, but are there subsets of the population that have particular unmet need or that may be, conversely, more amenable to treatment?

You talked about a risk stratification score that you developed. Maybe you can elaborate a little bit more on where the unmet need is greatest and which population may be most amenable to an RNAi therapeutic approach.

Answer – Heiner Wedemeyer: Obviously, from a clinical perspective, I have right now my interferon. I have used interferon on many patients, so the most urgent need is for those patients who are either intolerant to interferon or where interferon has already failed. Those patients are left with nothing, so I urgently need something.

From the overall clinical perspective, obviously we have many rather young patients who are in the age of within 20, 30, 35 and who have a pretty progressive course of liver disease. And the only option for these young individuals is actually liver transplantation.

You can imagine that if I would have something in hand that would reduce HDV replication, that would reduce HBs antigen replication, I would immediately use this, but particularly in these young adults with chronic advanced HDV infection who are at high risk of disease progression.

And where I can tell you it's no fun in the clinic to counsel these patients and to tell them -- when they ask, what can you offer me? And you say, well, nothing; just wait for your complication or your cancer and, if you're lucky, I may get an organ for you. And that's all I have. So this is really something where I need something new.

Answer – Pushkal Garg: That's really helpful. Another question that has come in is around -- you both talked about targeting HB surface antigen as a way to prevent hepatitis D or to treat or to cure hepatitis D. Can you -- maybe Dr. Wedemeyer and then, Laura, you can follow if you have anything to add.

What should be the target? We've talked a little bit -- Laura talked a little bit about targets in terms of what we would look for in HB surface antigen knockdown. But for hepatitis D, what should be the target level of hepatitis B surface antigen knockdown that's needed to clear HDV? And could even a small amount of residual surface antigen be permissive to HDV?

Answer – Heiner Wedemeyer: This is certainly something which needs to be -- the honest answer is I don't know whether there is a specific level which we still could tolerate and whether this may alter the natural course of disease. What is very important here for Delta is that we really need to get rid of S antigen in general. Not only to target, let's say, the viral transcripts, but also the S antigen which can come from integrated forms of HBV.

And this is, I think, crucial that the RNAi targets consider this as a potential source, which would be still sufficient to propagate HDV replication. So in my view, most likely we need really to suppress ***HBV*** as much as possible and also S as much as possible to have a clinical effect on Delta, but an exact threshold needs to be determined in clinical trials.

Answer – Pushkal Garg: Great. Laura, anything you want to add to that?

Answer – Laura Sepp-Lorenzino: That's right on. What we do know from preclinical studies is that both depending on the sequence that's integrated and what type of S antigen the protein can express, it may be sufficient to support HDV replication. So, yes, it will be important to be able to suppress with an RNAi drug both sources of S antigen, the integrated DNA and the CCC DNA.

So that being said, how much do we need to knockdown? I think it's -- right now, as Heiner clearly outlined, there are no therapies. So the lower bar would be can we knockdown 1 log of S antigen from both sources? And will -- that is expected to already be lead to a decrease in HDV RNA in viremia. Now that could lead to chronic treatment of HDV and control of the infection.

Now, getting better and more efficacious obviously would be better. Ultimately, if, via this mechanism, we can cure ***HBV***, we will also be curing HDV. But I think that we can walk before we run and first understanding the dose escalation. Would S antigen knockdown can lead to significant antiviral effects and then from there go what are the regimens, the combinations that we will lead to an effective ***HBV*** cure leading to an HDV cure?

Answer – Pushkal Garg: That's great, thank you. I think we have time for one last question. Just looking down the list; and maybe it ties into the last concept that you both were speaking about and this one's for you, Laura.

You highlighted the vision of functional cure in hepatitis B. Maybe you could just comment on what exactly that vision is and what does that mean? I don't know that we all understand fully what that concept is.

Answer – Laura Sepp-Lorenzino: Yes, there is a lot of discussion but also agreement on what we are envisioning as a functional cure. So what we are looking is after cessation of therapy it would be a demonstration of immunological control of infection, as reflected by the blood biomarkers with ***HBV*** DNA being negative, undetectable, but also the S and E antigens being undetectable. And this could be accompanied or not by the presence of anti-S antibodies.

Of course, everybody would want to see a further cure in which we had a sign of complete eradication of the CCC DNA and integrated DNA. But I think right now, given the state of the ***HBV*** drug development, achieving functional cure would be game-changing for many, many patients.

Answer – Pushkal Garg: That's great. Thank you, Laura, and thank you, Dr. Heine Wedemeyer. With that I'm going to turn it over to Josh.

Answer – Laura Sepp-Lorenzino: Okay. Thank you, Pushkal, and thanks to our speakers, Laura and Dr. Wedemeyer, as well as to all of you on the webcast for joining us today.

The replay and slides will be posted on the Alnylam website later today at alnylam.com/roundtables, and the transcript will follow shortly thereafter. You can also view that page to access any of the other roundtables from this year's series.

This concludes today's event. Thanks, everybody, and have a great day.
