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ALNY - Alnylam RNAi Roundtable: ALN-TTR Program Overview

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PRESENTATION

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

Good afternoon, everyone, and thank you for joining us for Alnylam's RNAi roundtable to discuss the progress we are making with our ALN-TTR program, which recently advanced to a phase I trial in patients with transthyretin-mediated amyloidosis.

I am Cynthia Clayton, Senior Director of Investor Relations and Corporate Communications for Alnylam. With me today are Barry Greene, our President and COO, and Dinah Sah, our VP of Research. I'll be turning it over to Barry shortly, who will provide you with a brief overview of our recent clinical progress, and then to Dinah, who will walk you through the status of the TTR program and the potential we believe this opportunity represents.

I would like to just take a moment to share with you the goal for our RNAi roundtable program. We have designed these to be in-depth presentations and discussions around key topics and value drivers of our business. We aim to be able to provide you with an opportunity to interact with the broader Alnylam team, as they share with you their particular areas of expertise.

We will be holding these sessions at various times throughout the year on other topics of interest. We hope that you can join us for those as well. Some will be onsite, as we have done in the past, and others will be virtual, as this is today.

We expect to wrap up this event by about 3 p.m. today. Online participants can find our speakers' bios as a link at the bottom of the page, and the online Q&A feature at the bottom of the webcast interface. Please submit your questions at any time, and we will address them at the conclusion of our presentation. As a reminder, we will be making forward-looking statements and we encourage you to read through our most recent SEC filings. And with that, I will turn it over to Barry. Barry?

Barry Greene - *Alnylam - President, COO*

Thanks, Cynthia, and good afternoon, everybody. It's a pleasure to be here to provide an update on our ALN-TTR program, a program we are very, very excited to have recently initiated our phase I.

Before I turn the call over to Dinah Sah, who's our VP of research and has been the Program Executive from the very beginning of the TTR program and has tremendous passion for this program, let me provide a quick overview of Alnylam.

As all are aware, Alnylam was founded on the breakthrough technology of RNA interference. And our goal from the very beginning is to develop a robust pipeline of RNAi therapeutics using the RNAi very powerful pathway. And in fact, we've done exactly that. We believe that RNAi therapeutics offers the potential of being the next product platform.

Our most advanced program is for the treatment of RSV infection. ALN-RSV01 is in a RSV infected lung transplant adult population and we are developing ALN-RSV02 for the pediatric opportunity. This program is partnered globally with Cubist and in Asia with Kyowa Kirin. Our next program is for the treatment of liver cancers, ALN-VSP. ALN-VSP is currently in a phase I ascending dose study. We are still accruing and still dose escalating and look forward to providing further updates on that program in the future.

As I mentioned, today's focus is on ALN-TTR for the treatment of TTR-mediated amyloidosis. Dinah will go into that program in a moment. What I'd like to say is that TTR for us represents an important opportunity to show human proof-of-concept in a patient population that desperately needs treatment options. And because we believe so much in the patient opportunity, the clinical opportunity, we've backed up ALN-TTR01 with ALN-TTR02, which takes advantage of the next generation liposomal nanoparticles.

Other programs that we have entering clinical trials in the next year or so are ALN-PCS for the treatment of hypercholesterolemia, by targeting a very important target, PCSK9, and our Huntington's disease program, partnered with Medtronic, to develop a novel drug device combination for Huntington's disease by targeting the Huntington gene itself.

Now, in this decade of RNA in general, RNAi therapeutics is really at the frontier of human proof-of-concept. As I've just highlighted, there are an increasing number of RNAi therapeutics in the clinical stages. I've been through ALN-RSV, which is an immunology opportunity, VSP, which is a systemically delivered oncology opportunity, and TTR. Across the industry, there's about 11 programs in clinical stages right now. And in the not so distant term, we should be seeing, across a number of companies and a number of applications, human proof-of-concept utilizing a broad range of technologies.

Now, over the last several years, having completed eight trials or ongoing trials, enrolled about 400 subjects and conducting studies in ten countries. It should be clear that we've significantly de-risked the regulatory and clinical approach, at least to initiate these clinical trials, and are very satisfied with the key milestones to date. That is the first human proof-of-concept in 2008 and the first systemic delivery program in 2009. That's our VSP program. So with that, let me turn the call over to Dinah Sah to take you through our TTR opportunity. Dinah?

Dinah Sah - *Alnylam - VP - Research*

Good afternoon. It's my pleasure to take you through the ALN-TTR program. I'll start with a brief introduction, and then I'll describe how we selected our lead siRNA molecule. I'll show you some of the exciting preclinical data that we have in vivo, including in a transgenic mouse model, of TTR amyloidosis. And then finally I'll briefly describe our phase I study design, ending with a summary and next steps for the program.

So, TTR-mediated amyloidosis, or ATTR, is an inherited disease with a very high unmet medical need. It's caused -- it's known to be caused by mutations in transthyretin, TTR. These mutations lead to amyloid deposits in multiple tissues, including importantly the peripheral nervous system and the heart.

Now, ATTR is an orphan disease affecting approximately 50,000 patients worldwide. The disease onset is relatively early in life. It strikes patients really during the prime of their lives, from the ages of approximately 30 to more than 60 years of age. It's fatal within five to 15 years. And the only treatment available, and only for a subset of neuropathy patients, is liver transplant, which is the current standard of care.

As Barry mentioned, we have ALN-TTR currently in clinical development. We initiated that trial earlier this month. And as a second generation program in development, we have ALN-TTR02. There are two major types of clinical presentation associated with TTR amyloidosis. And these are familial amyloidotic polyneuropathy, or FAP, and familial amyloidotic cardiomyopathy, or FAC. FAP involves the peripheral nervous system. And in particular the sensory and autonomic portions of the peripheral nervous system are impacted.

The autonomic neuropathy drives much of the substantial disability in the patients and leads to dysfunction of the gastrointestinal system, inability to control blood pressure, for example, and inability to control other important autonomic functions. Motor neuropathy appears later in these patients, as well as potentially cardiomyopathy.

FAP, the age of onset is relatively early, between the ages of 30 to 50 in Japan and Portugal, and in Sweden approximately 55 years of age or later. The prognosis and prevalence indicate the high unmet medical need here. The survival is approximately five to 15 years after prognosis. And the prevalence is about 5,000 to 10,000 patients worldwide.

FAC, the cardiomyopathy form, has significant impact on cardiac function, impacting the ability of the heart to conduct, leading to arrhythmias. It can cause restrictive cardiomyopathy and occasionally angina. This tends to occur in somewhat older populations of individuals, greater than 60 years of age. Again, median survival is quite poor, approximately five to 7.5 years after initial diagnosis. We estimate the prevalence of FAC to be approximately 40,000 patients worldwide.

So why have we chosen to target -- put the emphasis on TTR as a program? Well, we know that hepatocytes, the primary cell types in the liver, are the primary sites of TTR production. We also have very effective delivery of siRNA to hepatocytes with our current lipid nanoparticle, or LNP, platform. Given the target being extremely well validated with human genetics, targeting TTR through this -- our formulations that deliver siRNAs to hepatocytes in the liver clearly points to ALN-TTR as an important potential therapeutic for ATTR.

We formulate a chemically modified TTR siRNA in a [slight] lipid nanoparticle for systemic delivery. Now, both the mutant and wild-type TTR proteins are thought to be pathogenic. Liver transplant can stabilize or improve the outcome in FAP patients, in particular V30M mutation FAP patients. However, cardiac disease can be accelerated, we believe due to the increased production of wild-type ATTR. So targeting both the production of wild-type and mutant TTR is an important therapeutic strategy for the treatment of TTR amyloidosis.

So a bit of background on the biology of TTR. TTR exists as a tetramer in the circulation, approximately 55 KDa in size. It's known to bind and transport serum retinal binding protein and a minor fraction of serum thyroxin, T4. We know that in the case of the mutant form of TTR that when the mutant is a part of the tetramer, that the tetramer becomes destabilized. And then the monomers emerge, which then re-aggregate to form oligomers and then ultimately amyloid fibrils.

It's the oligomers containing the mutant form of TTR that are thought to be toxic and cause pathology in the periphery. Knockout data from genetically modified animals suggests that lowering TTR will be very well tolerated. These animals have a relatively mild phenotype with reduced levels of some of the proteins that TTR is involved with carrying in the circulation.

So next I'd like to turn to our data on ALN-TTR siRNA lead selection. We know that there are more than 100 mutations present in TTR, which are -- most of which are associated with pathology. Our siRNA targets a region outside of these 100 or so mutations, allowing us, therefore, to potentially affect TTR amyloidosis in all patients, irrespective of the type of mutant that they have. We target a region that's been common to both the wild-type and these mutant forms of TTR.

Our lead siRNA candidate was selected based on screening data in vitro. It's predicted to be, as I mentioned, broadly efficacious across all patient populations. Furthermore, we've confirmed that with regard to nucleotide polymorphisms that our target region does not fall in any regions identified associated with polymorphisms. Again, therefore, our drug candidate is predicted to be efficacious across all patients with TTR amyloidosis.

Our gene silencing is also highly specific. We know that our siRNA targets region or stretch of nucleotides that is highly specific for the TTR gene. There's known to be at least two mismatches with every other known human gene in the human transcriptome. And finally, we've designed our siRNA to avoid immunostimulation by introducing chemical modifications that are known to reduce the chances of immunostimulation, as well as increased stability of the molecule.

So the next slide shows our in vitro screening results, our initial single dose screen, where approximately 140 siRNAs against TTR were compared head-to-head at a single dose in HepG2 cells, which express TTR endogenously. We then looked approximately 24 hours after transfection of these siRNAs for reduction of TTR message. And what you can see in the bar graph is a number of these 140 siRNAs inhibited TTR message by at least 80%.

When we carried out dose responses on the selected subset of siRNAs that were effective in this initial screen by more than 80%, we were able to compare the potencies of these siRNAs in vitro and select our lead candidate, which has a potency of approximately 3 pM. So a very potent lead siRNA selected from these in vitro screens.

We also went on to confirm that this chemically modified TTR siRNA does not induce cytokine production or have immunostimulatory effect in human PBMCs. And the results are shown here for interferon alpha and TNF alpha. And what you can see is that when we look at the supernatants from these human PBMCs that positive controls and negative controls behave as expected, either inducing an interferon TNF alpha response for the positive control siRNAs, or not inducing response as expected for the negative control siRNA. Our lead TTR siRNA candidate was negative in this assay, as illustrated here.

So our TTR drug product, then, comprises an siRNA targeting TTR. And it has an IC50 of approximately 3 pM. It's a very potent siRNA. It's formulated in a lipid nanoparticle comprised of multiple components, illustrated in the cartoon on the left-hand side. This lipid nanoparticle formulation is a very robust delivery vehicle for targeting siRNAs to deliver.

And we've achieved hepatocyte specific gene silencing with this formulation, not only for TTR, but for a number of other genes across multiple species, as well, expressing hepatocytes. ALN-TTR02 is formulated with a second generation lipid nanoparticle, which provides us with improved potency as well as therapeutic index. It utilizes the same siRNA as ALN-TTR01.

So now I'll turn to some preclinical data in vivo with both ALN-TTR01 as well as with our next generation lipid nanoparticles utilizing the siRNA targeting TTR. We conducted a number of initial studies with a rodent siRNA analog. So here the TTR siRNA targets a region that's present in rodent or rat TTR. And what's shown here on this first slide is dose dependent silencing of TTR in the liver of rats.

So in this study, a single IV infusion of this rodent TTR analog was given to the animals, formulated in the same SNALP formulation as our clinical candidate. And we looked at liver mRNA levels approximately 48 hours later. And what's plotted below is the relative TTR mRNA levels normalized GAPDH and further normalized to the PBS group. And what you can see is that there's a dose dependent effect of the TTR siRNA, with an ED50 of approximately 0.3 mg/kg in rats. So a very potent siRNA formulation targeting TTR.

We went on to confirm that this silencing of the rodent message in hepatocytes translates into a reduction in circulating TTR protein levels in the rat. So here in the same experiment essentially we looked at the circulating levels of TTR approximately 48 hours after the IV infusion. We compared the post treatment circulating TTR protein levels, indicated by post the second of each of these pairs of bands in the Western blot and compared those to the [pre leads] from the same groups.

And what you can see is that if you compare the post versus the pre that there's a very substantial reduction of TTR protein, as assessed by this Western blot analysis, at doses ranging from 0.1 to 3 mg/kg. There was no effect of the control siRNA (inaudible) in the same formulation compared with PBS, as well as compared with the pre leads, as anticipated.

A hallmark of RNAi effects is a durable suppression of the target gene -- targeted gene. And so here we confirmed that with TTR siRNA that the reduction of TTR message in the rat is durable. And so this experiment, a single IV infusion of the same rodent TTR analog, I showed you the data in the previous slide, in the same SNALP formulation was given to the animals. And then at various time points after the administration, mRNA levels in the liver were monitored.

And what you can see is that it takes about three weeks for those message levels to come back to baseline level. So consistent with the RNAi mechanism, the effect of the siRNA targeting TTR is highly durable in vivo.

We next turned to a transgenic mouse model of TTR. This was done as a collaboration with Professor Maria Saraiva based in Portugal. And in this transgenic mouse model that she developed, the mice contained the V30M mutation human mutant form of TTR. We evaluated the ability of our clinical candidate, so now this is the siRNA targeting primate TTR, both human and nonhuman primate formulated in SNALP. This is our clinical candidate that's currently being tested in the phase I trial.

And what you can see is in this transgenic mouse model that on the left, both mRNA in the liver, as well as on the right, protein levels are suppressed in a dose dependent manner with ED50s of approximately 0.2 mg/kg in these transgenic mice. So our clinical candidate is not only is potent on the human mutant form of TTR, this V30M being the primary mutation responsible for familial amyloidotic polyneuropathy.

We also showed in this mouse model that the effect of ALN-TTR is durable. So we looked at the time course of silencing both message in protein following a single IV administration at 1 mg/kg. And what you can see is that both on the mRNA liver mRNA and serum protein levels, the effect was quite durable, lasting at least three weeks.

An important experiment, perhaps our most important data point to date in vivo is the effect of ALN-TTR in this transgenic mouse model on the accumulation of human -- mutant human TTR in peripheral tissues. So in this mouse model, again dev eloped by Maria Saraiva, she published and showed previously that TTR deposits accumulate in the same tissues that are impacted in clinical disease. In the peripheral nervous system goes through a ganglion sciatic nerve as well as the gut, including the stomach and intestine.

And so in this study we wanted to ask whether ALN-TTR could reduce these deposits of TTR in the peripheral tissues. The first experiment that we did was to assess prevention of accumulation of TTR in these peripheral tissues. And here three doses of ALN-TTR were administered every two weeks. And then two weeks after the third and final dose, immunohistochemical analysis of TTR deposition was used to assess the effect of ALN-TTR.

We compared the effect of ALN-TTR to a control siRNA targeting [vociferate] using the same SNALP formulation. And what you can see on the right-hand side in the micrograph is that in the animals treated with ALN-TTR there's no significant detectable TTR amyloid deposits, as shown on the left-hand side as brown deposits.

When we treat the animals with a control siRNA, again targeting vociferate in the same formulation, they have the anticipated levels of TTR deposits, which show up as a brown stain in this immunohistochemical analysis. On the left-hand side we've quantified the TTR tissue levels, which shows again the dramatic reduction in TTR immunoreactivity when we administer ALN-TTR to these animals.

The next experiment that we did was to assess whether we could impact preexisting deposits of TTR in peripheral tissue. So we essentially looked for the ability of ALN-TTR to cause regression of these preexisting deposits. So here we treated older mice, older transgenic mice that already had TTR deposits in these peripheral tissues. We treated these mice with six doses every two weeks. And then about a week after the sixth and final dose, assessed whether they had TTR deposits in these peripheral tissues.

And as illustrated on the right-hand side in the micrograph, you can see that after treatment with control siRNA, these animals have a substantial amount of TTR deposits in the dorsal root ganglion, for example, as shown by the brown staining. However, after treatment with ALN-TTR, there's no detectable TTR immunoreactivity.

And when we quantify that, as shown in the bar graph on the left, what you can see is there's a very substantial reduction, regression actually, of TTR deposits in these clinically relevant peripheral tissues. So very exciting data, illustrating the potential for our drug candidate to actually cause regression of preexisting TTR deposits in peripheral tissues.

And then finally, in vivo with ALN-TTR01, we confirmed that the results that I've been showing you in rodents extends in nonhuman primates. So here we assessed the ability of ALN-TTR to silence TTR mRNA in the liver of nonhuman primates following a single IV infusion. And what you can see is this dose dependent effect of ALN-TTR in reducing TTR message in the liver, with an ED50 of approximately 0.3 mg/kg in contrast to the control siRNA, (inaudible) siRNA in the same formulation as shown on the left in purple.

At this point I'll turn to some exciting data we have on our second generation with the nanoparticle formulation, both in the rodent and nonhuman primate. So here, using the same siRNAs that I showed you previously, we're now formulating them in

our second generation LNPs. And what you can see in this first slide, using the rodent siRNA targeting TTR, is a dose response evaluating liver levels of TTR mRNA. And what's shown here is an ED50 of approximately 0.03 -- or less than 0.03 mg/kg in the rodent. And so a highly potent silencing with our second generation LNP.

In the nonhuman primate we showed that the silencing extended this potency -- enhanced potency of LNPs, next generation LNPs extended to nonhuman primates. So here, after a single dose, the ED50 is less than 0.03 mg/kg on liver levels, liver mRNA levels of TTR, as shown on the left.

We also evaluated effects on circulating TTR protein in the nonhuman primate study, as shown on the right, as well as looked at durability persistence of reduction of circulating TTR protein. What you can see is after a single administration at 0.03 mg/kg, in the light blue circles, and we get about 50% reduction of circulating TTR protein and that this is quite durable, partially returning towards baseline after approximately three and a half weeks post dosing.

So those are the preclinical in vivo data on ALN-TTR01 and ALN-TTR02, which are very exciting and illustrate the potential of these drug candidates for the treatment of TTR amyloidosis. So, at this point I'd like to turn to our phase I study design, as shown on this next slide. Our ALN-TTR01 phase I clinical trial is a multicenter, randomized, blinded, placebo-controlled, dose escalation study.

We're planning to treat approximately 28 patients with -- that have TTR amyloidosis, including polyneuropathy and cardiomyopathy forms. And the trial is being conducted in Portugal, Sweden and in the UK. Our primary objective in the phase I trial is safety and tolerability. And secondary objectives include plasma and urine PK as well as pharmacodynamic activity of the drug on TTR serum levels.

So in summary, then, ALN-TTR is -- comprises an siRNA targeting TTR, both the wild-type and all mutant forms of TTR. It's a chemically stabilized duplex that's formulated in a lipid nanoparticle formulation, SNALP formulation. We hypothesize that our RNAi therapeutic will, by inhibiting both the mutant wild-type TTR mRNAs produced in the liver, that we will decrease amyloid deposition in peripheral tissues and facilitate clearance of amyloid from these tissues, thereby either halting progression or improving function of the various organs and tissues impacted by TTR amyloidosis.

We're targeting both familial amyloidotic polyneuropathy, as well as the cardiomyopathy forms, which has the potential of impacting approximately 50,000 patients in total worldwide. We initiated our phase I trial in July, earlier this month, and are advancing our second generation formulation of TTR -- ALN-TTR02 in development.

Our next steps, then, our summary is shown here. And again, it's really based on the very exciting in vivo data that we have, not only in rodents and nonhuman primates, but also in the V30M transgenic mouse model that we believe that this molecule, this drug product has tremendous potential for therapeutic efficacy in the clinic. So, with that, I'll close on the update of the TTR program.

QUESTIONS AND ANSWERS

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

Great. Thank you very much, Dinah. We will now open it up for your Q&A. And as a reminder, please submit any questions you have in the Q&A tab at the bottom of the webcast screen. We do have some questions that have come through and I'll move to the first question. Can you envision ALN-TTR02 replacing ALN-TTR01 once you are ready to move into phase II?

Barry Greene - *Alnylam - President, COO*

Very good question. So as I highlighted at the beginning, we believe significantly in the opportunity in treating transthyretin amyloidosis, and therefore have enthusiastically moved TTR01 into the clinic. If TTR01 has the kind of effects that we hope it does, that we've designed our clinical trial around, it's very possible that ALN-TTR01 continues to progress forward into phase II and beyond.

That being said, because of the opportunity and because we've made such significant improvements using second generation liposomal nanoparticles, we thought it prudent to develop ALN-TTR02. That really gives us future optionality. That doesn't necessarily mean that that becomes the program moving forward, but we, in fact, based upon what we see in the clinic, have options of moving forward with 01 or 02.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

Great. The next question is what is the dose limiting toxicities of lipid nanoparticles?

Barry Greene - *Alnylam - President, COO*

Let me provide some broad context and maybe turn over to Dinah for some more details. So the question was tox of liposomal nanoparticles. But when we think of RNAi therapeutics encapsulated in liposomal nanoparticles, it's important to think of the product in totality. That is both the siRNA and the liposomal nanoparticle formulation, recognizing that all components of the total product have toxicological potential toxicological effects.

So it's not just about liposomal nanoparticles, it's about the whole program. And frankly, with both VSP and now TTR in the clinic, we'll see in man, in our own studies, what the dose limiting toxicities are. What we know preclinically, particularly nonhuman primates, is the primary organ of toxicity is the liver. And we also know, based upon the history of using lipids in the clinic, that one needs to be wary of intravenous reactions, or dosing reactions, when you use this systemically. So those are things particularly we are looking for.

In the clinical experience thus far, which has been Tekmira in their ApoB program, we know that, in fact, they did see some flu-like symptoms, immunostimulatory effects. Again, considering the overall package of both SI and LNPs. Dinah, you want to add to that?

Dinah Sah - *Alnylam - VP - Research*

Yes. I think our preclinical data suggests that we have very good therapeutic index with ALN-TTR01. So the potent siRNA together with what we know about the toxicity of liposomes gives us a very reasonable path forward into the clinic with ALN-TTR01. And of course, as we spoke about with ALN-TTR02, the potency is enhanced by approximately tenfold in our preclinical in vivo studies and the therapeutic indexes is correspondingly wider as well.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

Great. Another question here. What are the hypothesis of the mechanism for regression?

Barry Greene - *Alnylam - President, COO*

Yes, Dinah, you want to take that?

Dinah Sah - *Alnylam - VP - Research*

Yes. We're currently doing studies to look further into the potential mechanism of regression. But the hypothesis is because we've inhibited the synthesis of TTR, the production of TTR in the liver, that over time the deposits, the clearance mechanism, the natural clearance mechanism for the deposits predominates and allows the amyloid deposits to regress and become undetectable by our immunohistochemical methods.

Barry Greene - *Alnylam - President, COO*

Right. And what is very interesting, and Dinah highlighted this in her talk, is that some of the most striking in vivo data we have is actually in the transgenic mouse models where the hypothesis that many of the thought leaders had about what was possible was at least proven out in this animal model. And quite frankly, in very dramatic fashion.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

Great. Next question, what mean relative reduction from baseline would you like to see in this phase I study with therapeutic doses?

Barry Greene - *Alnylam - President, COO*

Yes, so, I'll remind you that the phase I study is a safety and tolerability study with ALN-TTR01. So we're really focused in this patient group at single -- an ascending dose study and the doses we've outlined and ensuring both safety and tolerability.

That being said, because it's measurable we will look at TTR levels. And again, because it's an ascending dose, we really have to pay the most attention to the patients at the top doses where we believe we'll have the most dramatic effect. And to be frank, we'll see when we get there across how many patients and what kind of dose reduction levels we're looking at. Clearly, if we see in man what we've seen in animals, we have a significant success.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

A somewhat related follow-on question is what is the current best estimate for the level of serum TTR reduction that tips the balance toward (inaudible) clearing of deposits in various tissues?

Barry Greene - *Alnylam - President, COO*

Dinah, you want to take that?

Dinah Sah - *Alnylam - VP - Research*

I think based on other types of amyloid doses, our belief, as well as the belief of thought leaders in the field, is that approximately 50% reduction of circulating TTR would have the potential to lead to clinical benefit. So certainly the thought is that we don't need to completely eliminate circulating TTR, but rather a partial lowering has the potential for leading to some therapeutic benefit.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

There's been a request to discuss the overall regulatory strategy.

Barry Greene - *Alnylam - President, COO*

Yes, so, the regulatory strategy is not necessarily unique here. What we have at our advantage is a patient population with a significant unmet medical need. And because of that, there's been tremendous enthusiasm from the regulatory agencies to engage us and scientifically and medically understand what this clinical trials look like.

We've conducted trials and will conduct trials in the centers that have the most patients. This is where the patients live, in Portugal, Sweden, UK and potentially some other countries. And then post phase I, depending on the data, we will drive what future clinical trials look like with either ALN-RSV01 or 02.

We do believe, based upon work done by [Folgarex], a company studying a TTR-mediated amyloidosis product using quite different mechanism, that there've been some very interesting and appropriate endpoints outlined for approval that should give us good predecessor in engaging regulatory authorities when we do get to the approval stage.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

So there's a segue there. We've received a question about how our program compares to that of Folgarex.

Barry Greene - *Alnylam - President, COO*

Yes, so, we had the good fortune, frankly, in studying transthyretin-mediated amyloidosis of following another company. And the benefit to us is that Folgarex has done a very good job highlighting and assembling the key opinion leaders, the centers, and uniting them to do a study that had frankly never been done in this patient population before. And we've gotten great advantage from that.

I can't speak in detail to the data of Folgarex. You'd really have to ask them what the data say and where they are. I know the people are quite enthusiastic about some of the data. But you really need to ask them. The benefit to us is that they've identified a path, they've identified a set of clinical regulatory endpoints that give us an opportunity to follow.

I do know we've gotten questions that ask what if Folgarex is approved in the market before you get there. And that is only a benefit to the patients and frankly something we hope happens for the benefit of these patients, and a benefit to us. As you can imagine, in a horrific disease like that -- like this that is universally fatal, the opportunity of using one or more drugs that turns this into a chronic disease and keeps people alive without these comorbidities for an extended period of time is of benefit to the patients, clearly, and to all companies involved.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

Great. Question. Why does the cardiomyopathy get worse with liver transplant?

Barry Greene - *Alnylam - President, COO*

Dinah, you want to take that?

Dinah Sah - *Alnylam - VP - Research*

We believe it's -- that it's likely due to the production of wild-type TTR from the transplanted liver that then contributes to the preexisting deposits that are present in the patients. So and that this actually, in some cases, and particular in the context of cardiomyopathy, can actually accelerate pathology.

Barry Greene - *Alnylam - President, COO*

And just to back up a second and to highlight where the question's coming from, as we all know, in a very small subset of primarily FAP patients, the only approach that's been successful to date is liver transplantation. And as Dinah highlighted, while that seems to help the morbidities associated with FAP, it seems to accelerate the issues associated with FAC, or the cardiomyopathy.

That being said, because it hasn't been done for years and it's a small patient population, that fact is not a definitive fact. What we've been told by the thought leaders, though, is they believe that to be the case. And in fact, we have an opportunity with our drug of treating both pre and post liver transplantation because of that issue.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

When do you realistically expect ALN-TTR02 phase I to commence and what is your best estimate to completion and reporting of data from the current ALN-TTR01 phase I?

Barry Greene - *Alnylam - President, COO*

So, as we've highlighted a number of times, we are very enthusiastic to initiate TTR01 program in multiple sites around the world and aligning the protocol so we have common protocols per site. To be frank, we'll have to get going with this trial and see what accrual looks like before we can provide any specific projections either of 01 or 02.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

Next question. Would you consider filing for subpart H and using TTR reduction levels as a surrogate endpoint?

Barry Greene - *Alnylam - President, COO*

So, the regulatory approach, the expectation that I think would be most appropriate to set with any clinical trial, including a clinical trial that's an orphan drug trial, is an expectation that a robust phase III trial may be required for a regulatory approval. So I wouldn't guide about any kind of accelerated approval or subpart H approval.

As I've highlighted, we are benefited by a clinical study going on before us that's outlined a reasonable regulatory path. That being said, the data always drives what happens at the regulatory front and we really need to see the data before we can provide further guidance.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

On a related topic, would the FDA expect some form of comparability studies for a change of formulation from TTR01 to TTR02?

Barry Greene - *Alnylam - President, COO*

As we've highlighted, what TTR02 has done is taken advantage of the next generation of liposomal nanoparticles, which translates to far less drug required to create the kind of knockdown that we've seen in animal models. And then we have to engage the regulatory authorities when we get to the point, if we decide to, to move from 01 to 02. It's far too soon, having just initiated 01, to provide any real perspective or guidance on that.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

Is your estimated prevalence based on frequency of mutations or based on clinical diagnoses?

Dinah Sah - *Alnylam - VP - Research*

It's really a combination of both. And for -- of course, for FAP, it's known and well documented that the V30M mutation causes -- is responsible for FAP in approximately 90% of the patients, the vast majority of patients. And those numbers, those estimates of prevalence are much more solid.

For cardiomyopathy, there's much less data around the prevalence of both FAC that can be actually attributed to mutations in TTR. So we've combined sort of estimates of the prevalence of the V122I mutation as well as numbers of patients with cardiomyopathy to arrive at the much more approximate of approximately 40,000 for FAC population.

Barry Greene - *Alnylam - President, COO*

Right. And like many diseases that have not been commercially studied, as commercial entities, Folgarex, which you've talked about, and ourselves get into this disease, we're discovering more and more information, a lot better clarity as the program progresses. That being said, we're well aware that this is an orphan disease and a Genzyme-like opportunity for us in this more focused patient group.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

Can you comment on any challenges of patient accrual for TTR?

Barry Greene - *Alnylam - President, COO*

So what we've chosen to do is initiate phase I trials in the best centers in the world that attract the TTR patient. So the thing we know about is it's an orphan disease, and therefore have certain incidence and prevalence of this disease. But we're focused on opening multiple centers and the best in the world to appropriately accrue the trial. I don't see any real challenges with clearly initiating, which we've done, and completing this phase I study.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

Moving now to some of the preclinical work, what is the higher number of doses given in preclinical animal models, and have you measured liver enzyme levels in animals?

Dinah Sah - *Alnylam - VP - Research*

So, in the transgenic mouse models, we've gone up to 3 mg/kg in the dosing. Those -- the studies that I showed looking at prevention of deposits, and then also regression of deposits as well as the initial silencing studies looking at mRNA and proteins, went up to a top dose of 3 mg/kg. And of course there our main interest was assessing the pharmacological effect.

So we started with dose responses to establish that we were in the right range, to confirm that we were in the right range, given that this was a mutant form of TTR and that we were doing these experiments in the transgenic mouse model. And then we went on and picked the dose -- an initial dose for studying the prevention and then regression of the amyloid deposits. We're continuing these studies and doing additional work looking at additional doses as well as other endpoints.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

So, then, from there can you comment on the range of doses that were selected for the phase I trial and how they compare to those?

Barry Greene - *Alnylam - President, COO*

Sure. So we -- the phase I trial of the single ascending dose trial in approximately 28 patients, as we talked about being conducted in Portugal, Sweden and the UK. And we selected the clinical doses based upon both the rodent and the nonhuman primate preclinical dose. I'll remind you, in nonhuman primates we saw an ED50 at 0.3 mg/kg.

And when we think about allometric scaling and the need to prudently and appropriately, safely study this drug in man, we believe we've picked the right starting dose and the right ascending dose to see safety and tolerability, the potential effects (inaudible - background noise) that I talked about. That being said, as we -- as we escalate doses, if we feel the need to increase dose levels, we certainly have the safety profile to do so and can go to higher doses with a protocol amendment as the trial moves on.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

So following on that, can you tell us the dosing schedule titration schedule for the phase I trial?

Barry Greene - *Alnylam - President, COO*

So, it's a classic single ascending dose trial. We haven't given lots of details about numbers of patients [per core], but we have given details about the dosing levels. And there are patients on drug and patients on placebo. We'll be comparing those, monitoring for safety and tolerability and escalating in the appropriate fashion.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

So does TTR make use of the same SNALP formulation as VSP?

Barry Greene - *Alnylam - President, COO*

So, ALN-TTR01 is using the first generation liposomal nanoparticles, SNALP, similar to VSP. So the answer to that is yes. And as I talked about, ALN-TTR02 is taking advantage of the next generation of LNPs, which have ED50s at dramatically lower levels.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

What do you still need to understand about TTR02 that you already know about TTR01?

Barry Greene - *Alnylam - President, COO*

So, because TTR02 used the same sequence with the same modifications and it's about a more potent delivery, really what we have to do is complete the standard GLP tox studies and move the program forward. There's no specific unknowns with 02 that increase the risk profile, that we know of today.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

And in our remaining time we've got two more questions. The first is are you in contact with TTR patient groups?

Barry Greene - *Alnylam - President, COO*

Absolutely. I mean this is -- this is a horrific disease with a set of patients that are in desperate need of therapies. As we talked about, the only help for these patients that's used, and it's used very little, as you can imagine, is liver transplant, which has huge cost and huge challenges associated with it. So we are talking definitely to patient groups.

We can tell you that in a number of meetings and based upon the data, the patients are very enthusiastic about ALN-TTR01. In fact, incredibly enthusiastic that RNAi is being used here. Because when you think about it, this is a disease caused by too much bad TTR and we're stopping it from being made. That's exactly what you want to do in this kind of patient population. And the proof point is that when you remove the unhealthy liver and replace it with a healthy liver, the morbidity -- the comorbidities do improve.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

And our last question is where might regulatory filings occur for this program?

Barry Greene - *Alnylam - President, COO*

So, regulatory filings in terms of initiating phase Is have occurred in Portugal, Sweden, the UK, and may occur in other countries that have significant patient populations, US, France, Brazil, but more on that later as the trial gets going.

Cynthia Clayton - *Alnylam - Senior Director - IR and Corporate Communications*

Great. All right, well, thank you, everybody, for dialing in. we hope that this was helpful. The audio as well as the slides will be on our website if you would like to refer to them in the future. Thanks very much. Bye-bye.

Operator

Ladies and gentlemen, we thank you for your participation in today's conference. This concludes the presentation. You may now disconnect. Have a great day.