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ALNY - Alnylam Pharmaceuticals Inc "RNAi Roundtable" Webcast Series: Early Stage RNAi Therapeutics Pipeline

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PRESENTATION

Operator

Good morning, everyone, and thank you for joining us today for this RNAi Roundtable, where we will be discussing some of our early-stage investigational RNAi therapeutics programs. I'm Josh Brodsky, Director of Investor Relations and Corporate Communications at Alnylam. I'm joined today by Vasant Jadhav, Vice President of Research; Josh Friedman, Senior Director of Clinical Research; and Tanya Fischer, Vice President of Clinical Development. In just a moment, I'll hand it over to Vasant, but let me start quickly with a few brief comments.

Today's RNAi roundtable is part of a series of roundtable webinars that we'll be hosting this summer and early fall to review progress across our various programs. Today's event is expected to run approximately 60 minutes. Vasant will moderate a Q&A session at the conclusion of the presentations. If you'd like to submit a question, you can do so at any time during the event by typing your question in the 'Ask a Question' field. Finally, as a reminder, we will be making forward-looking statements during the webinar, and we encourage you to read our most recent SEC filings for a more complete discussion of risk factors.

And with that, I will now turn it over to Vasant.

Vasant Jadhav

Thank you, Josh, and hello, everyone. We are very happy to be sharing these exciting updates with you today. Okay. So to provide some context here, as most of you know, Alnylam has been the leader in advancing RNAi therapeutics as a new brand, a new class of innovative medicines. RNAi is a powerful approach to treat human diseases. It is what we have been focused on since our company was founded 18 years ago. At Alnylam, we are proud to have pioneered the translation of this technology from Nobel prize winning science into commercial products, with many, many more on the horizon, with the potential to have transformative impact on patients with a variety of diseases around the world. And I would say, it's no longer just a potential that we have been saying for so long because now it's real. We have 2 approved drugs and many on the horizon.

At Alnylam, we have built an industry-leading pipeline with 11 and soon to be 12 programs in clinical development, including 6 that are in late stages of clinical development with 2 programs that are currently in registration. These late-stage programs are the ones which we believe can fuel continued growth for Alnylam in the next few years and help build Alnylam into a top 5 biotech company.

We also have several additional programs that are in earlier stages of clinical development. In addition, and very importantly, Alnylam has built a product engine that is capable of generating 2 to 4 new INDs per year for sustainable innovation. Our pipeline programs cover a range of therapeutic areas including in the rare disease space as well as diseases that are far more common or even global in nature. What is really exciting is that this homegrown R&D engine that laid to the development of this organic pipeline, we can continue to apply it going forward. And we can now do that with not just liver targets but also now with genetically validated targets in CNS, in eye and lung. Using this product engine, we have built an exciting portfolio of over 20 preclinical programs across these 4 tissue types, out of which we plan to advance 2 to 4 new INDs per year.

What is also important to highlight is that our pipeline is now expanding beyond rare disease indications, programs that we describe as genetic medicines and generally afflict thousands to tens or even hundreds of thousands of patients to include much more prevalent diseases, with patient estimates ranging in the tens of millions to hundreds of millions. We've been really emboldened by the growing safety database with our conjugate platform, notably, experienced from the Phase III studies of inclisiran, which have provided the largest demonstration to date, suggesting there is no systematic evidence for platform-specific safety signal for our GalNAc conjugate sRNA. These results have greatly strengthened our conviction for the future potential of RNAi therapeutics in large population diseases like the examples, which are shown on the right side of this slide, including

cardiovascular, metabolic, infectious diseases and CNS and ocular diseases. It's really opening up the space in this area. In just a few moments, you will hear about our exciting effort developing in investigational RNAi therapeutics for the treatment of NASH, a highly prevalent liver disease. After that, we will turn to our initial efforts advancing RNAi therapeutics for CNS diseases, where we have the opportunity to pursue both rare disease indications as well as highly prevalent diseases with tremendous unmet medical need. With so many programs in our preclinical portfolio, for today, we are highlighting 3 of them here. So just wanted to put that out there.

So to kick things off, we'll hear from Josh Friedman, who will talk about our ALN-HSD program as a potential treatment for NASH. Josh?

Joshua Brodsky - *Alnylam Pharmaceuticals, Inc. - Director of IR & Corporate Communications*

Thank you, Vasant. And I'm delighted to be here this morning to talk about one of those highly prevalent diseases that you just mentioned, and that's NASH. NASH is a subset of a broader category called nonalcoholic fatty liver disease or NAFLD. And NAFLD, including NASH, really is the liver manifestation of an even broader problem, which is now nutrition, specifically overnutrition, in developed countries; and in the liver, that leads to the accumulation of fat in hepatocytes, as illustrated by the white areas in the histologic section shown in panels A and B. NASH, nonalcoholic steatohepatitis, is a subset of NAFLD in which there's progressive potentially severe disease. And it's associated, in addition to the fat in the liver, with evidence of liver cell damage, as illustrated by the arrows in panel A, and by progression of fibrosis, illustrated by the blue staining in panel B. And it's the fibrosis that's really a major concern because it's the most tightly associated feature of NASH with morbidity and mortality. As Vasant mentioned, this is a highly prevalent disease, as illustrated in panel C of the figure.

In the United States, about 25% of adult have fatty liver disease, which is almost 100 million people, and the proportions are similar in other developed countries. About 1/4 of those will develop NASH with evidence of liver cell injury and inflammation, and about 1/4 of those, which amount to about 3 million people in the United States will have advanced fibrosis. Advanced fibrosis is a threat to human health because it's associated with the consequences of portal hypertension, progressive liver failure and hepatocellular carcinoma. And in fact, NASH is projected to be the leading indication for liver transplant in developed countries within the next 10 years. So this is a prevalent problem with a high degree of medical need, and yet there are no approved medical therapies. There is an effective treatment, it's weight loss. Weight loss is effective, but as we all know, it's difficult to achieve, and it's not durable. There is a great need for finding new pharmacologic targets for NASH.

What I'll talk about in the next couple of slides is a scientific basis for a target that we're going to discuss, called HSD17B13, and for short, we'll just call it HSD because it's such a mouthful. So HSD was discovered as a potential target for NASH through nonbiased genome-wide association study. These take advantage of a global natural experiment through genetic variation and testing that -- the association of variations with human disease. HSD first came to light because a variant in HSD was discovered to be associated with protection from elevated ALT, and ALT is a serum marker of liver injury. A major breakthrough came in 2018 in a paper in the New England Journal, and we have one figure from that paper illustrated here. And what was found was that the variant in HSD was associated with a decreased risk of nonalcoholic liver disease and a decreased risk of nonalcoholic cirrhosis, both illustrated in the red box.

In the subsequent paper, not shown here from last year, looking within the population of individuals with NAFLD, the variant was associated with protection from those same histologic features we looked at in the previous slide, specifically the inflammation and liver injury seen in NASH. So the power of this genetic analysis is tremendous because it gives us -- before anyone has developed a drug or run an interventional trial, it gives us a cause or relationship between the gene and the disease. What it doesn't tell us is the mechanism of that relationship, but we can't get some clues. So we know that this particular variant disrupts a splice site, and that splice site leads to a frame ship mutation, which converts from the normal wild-type mRNA isoform A to isoform D. And we can consider isoform D to be nonfunctional because it's both present at very low levels because it's eliminated through nonsense mediated decay, and because any protein that results from that isoform is enzymatically nonfunctional. So what we know then is that, with increasing dose of this variant, as illustrated in the left in the figure in the middle of the slide, there is a decreased level of the normal mRNA. And that's accompanied by a decrease in the levels of the normal protein illustrated by the blue columns in the figure to the right. So this leads us to recognize this as a potential perfect match for an siRNA compound. Because just as the genetics results in a loss of a normal mRNA, we can mimic that with siRNA mediated knockdown of the mRNA with the hypothesis being that this will be therapeutic in the context of NASH. So we know a little bit more about the loss of function generated by this variant, but we still don't know the full picture from a molecular mechanism.

In the next couple of slides, I'd like to give some clues, which don't answer all the questions but point us in a direction that can be explored in future studies. The first of these comes from an analysis of metabolomics in the liver, comparing people who carry this variant in HSD with those who do not. And what was found with that within the liver, those who have the protective variant had elevated levels of phospholipids, specifically species of phosphatidylcholine and phosphatidylethanolamine. The same study also found evidence of decreased inflammation as measured by mRNA and plasma cytokines. And just as important, they eliminated some potential mechanisms by finding that patients with the variant did not have any difference in hepatic free fatty acids, de novo lipogenesis or in fat tissue lipolysis or insulin sensitivity.

The second clue comes from related molecules, oxidized phospholipids. And in this case, it's been known for some time that they are elevated in NASH. And that's illustrated in the figure on the left, in which the bottom row includes staining for oxidized phospholipids. And you can see there that even comparing NASH to nonalcoholic fatty liver disease without NASH, there is a distinct difference and that the elevated oxidized phospholipids are present in NASH and not in just fatty liver disease, and they are also present in NASH with cirrhosis.

As you can see on the right, the levels of liver oxidized phospholipids go up with degree of fibrosis. And in the plasma, it appears to be a pretty good biomarker because they are elevated in NASH compared to NAFLD and in NASH cirrhosis, as shown in 2 different populations in the figures on the right.

So that's an association of potential biomarker. Functional data comes from mouse studies in which an antibody that neutralizes oxidized phospholipid is protected in that model. So we have some clues pulling oxidized phospholipids and phospholipids in general, but we don't yet have the full picture, but future studies, we'll explore this.

So I've shown so far that we have genetics pointing us to HSD as potential target. To test this, we need to develop a molecule. So what this slide encapsulates is a great deal of nonclinical work developing this candidate and testing it nonclinically. The image shows the result of knockdown of HSD17 with ALN-HSD, sRNA targeting this gene, in obese nonhuman primates. So not only are they primates like us but they are obese modeling the intended target population. And as you can see after a single dose, there is potent knockdown, 80% or 90%, depending on the dose extending out to day 42. Another NHP data, not shown in this slide, we have evidence that there is durable knockdown beyond this time point. Just as important, no preclinical toxicity of concern has been observed, which gives us high safety margins for future clinical development.

So what does that development look like? At this point, we are planning to file a CTA application in the middle of this year, with a planned Phase I start later this year, and looking beyond that, a plan for an initial clinical POC in 2021. What I'd like to do in the next slide is give you a high-level view of what the Phase I program is designed to look like. It's not a completely straightforward Phase I design. It includes a Part A and a Part B in NASH patients. The part A does include single ascending dose cohorts. It also includes a cohort, which is A5 on the top right, that includes liver biopsy, pre dose and post dose. And this is necessary because one of those challenges of HSD that I mentioned earlier and that we don't fully understand the molecular biochemical mechanism. And so we don't have a readymade peripheral marker to measure PD. And HSD is not a secreted protein, so we can't measure knockdown of the protein in the periphery. So the only way that we can measure target engagement PD that we have at the moment is by measuring reduction of mRNA in liver biopsy or reduction of liver -- protein in liver biopsy. So we will explore that in one of the healthy volunteer cohorts. There will also be 2 Japanese subject cohorts, as a matter of efficiency looking forward towards recruiting Japanese subjects in later clinical development.

Part B includes NASH patients because we've recognized that we are using a liver-targeted siRNA in the context of the liver disease. And in that context, we may see different PK/PD in NASH patients than in healthy volunteers. We also want to test 2 doses, multiple dosing in NASH patients to better model what we anticipate in later stages of development. There are 4 cohorts planned, 3 of them have a biopsy 3 months after the second dose intended to fall within the period of maximal knockdown. So we'd like to understand the relationship between dose and maximal degree of knockdown. One of the cohorts has a later biopsy. So in addition to understanding maximum knockdown, we could also understand the kinetics of recovery for knockdown. As illustrated in the bottom left corner, of course, the primary endpoints of this whole study are safety and tolerability. But as I've indicated, key secondary endpoints will be understanding PK and PD of ALN-HSD. And as I mentioned earlier, we're going to take advantage of this study and the samples from it to discover new potential biomarkers of HSD of ALN-HSD pharmacodynamics. And of course, because we will be impatient, we'll be looking at histologic markers of clinical efficacy as well as exploratory disease biomarkers

So to summarize, I hope I have shown that nonalcoholic steatohepatitis, NASH, is an important disease that can lead to progressive fibrosis, cirrhosis and hepatocellular carcinoma with a very large unmet need, with no existing medical therapy. The science, namely homogenetics, identifies HSD as a novel target for NASH, based on the finding of loss of function in association with protection from liver disease and injury. And this is the loss of function that we can mimic with siRNA. We've developed such an siRNA, ALN-HSD, which is an ESC+ GalNAc-siRNA conjugate, which targets HSD, specifically in hepatocytes, with the role of -- with the plan of reducing hepatic inflammation injury and fibrosis.

I've summarized CTA-enabling preclinical work that has been completed with no preclinical toxicity of concern observed and high-safety margins, which puts us on track for a CTA filing in the middle of this year and a Phase I start later this year.

Thanks for your attention. I look forward to discussing questions later. And in the meantime, I'm happy to turn it over to Tanya Fischer, who is going to elevate our discussion from the level of the liver up to the spine and the central nervous system.

Tanya Fischer

Thanks, Josh. Hi, everyone. I'm Tanya Fischer, the Vice President of Clinical Development here at Alnylam, and I'm very excited to talk to you today about our efforts in developing RNAi therapeutics for central nervous system diseases. The prospect of RNAi as a therapeutic intervention provides an opportunity to treat several diseases for which effective options are currently unavailable or limited. In particular, RNAi-based therapies are being investigated for diseases affecting the central nervous system, CNS, including sporadic and genetic neurologic disorders, which has posed challenges to translational scientists and clinicians for years. In fact, there are a number of CNS diseases that are genetically validated, inherited and likely caused by abnormal protein production and accumulation. An example of such neurodegenerative disorders, many of which have no currently approved disease-modifying therapies, include things like Alzheimer's disease, Parkinson's disease and Huntington's disease among many others. And given that the majority of diseases affecting the human population involve some form of aberrant gene regulation, the potential use of siRNA as therapeutic agents is extremely attractive as it allows for selective target knockdown of gene expression with an impact across a variety of diseases, and it also has the potential to be the next frontier for therapies. Also, based on preclinical studies, we expect superior potency, duration and systemic safety profile versus other therapies in development, like the ASO. And lastly, using siRNA to treat genetic liver conditions has shown to be an approach that works. We expect that learnings from our liver programs will translate into benefits in this organ system as well, including things like potency, durability, specificity, and of course, safety.

The first target we've selected is amyloid precursor protein or APP. Rare genetically validated diseases are an important focus for our CNS platform and that they will not only allow therapies to be developed in patient populations where there is a great unmet medical need but also provide us with information to help us determine whether they may be used to treat more common disorders. So when we think about developing ALN-APP, we are initially pursuing treatments for 2 rare neurologic diseases, specifically hereditary cerebral amyloid angiopathy or HCAA and autosomal dominant Alzheimer's disease or ADAD. HCAA is a disease where patients develop intracerebral hemorrhage, which can manifest like a stroke and can ultimately be fatal. HCAA is considered to be an orphan disease. There's only about, like, 400, 500 patients around the world. And we feel like this is a unique, genetically validated aspect of APP that we can address with an RNAi therapeutic. Now the important thing here is that proof-of-concept in this setting could also lead to a much greater expansion into a bigger opportunity, which is not rare and not orphan, specifically sporadic CAA. And that is through the amyloid angiopathy pathway itself, which occurs sporadically in people of 70 to 80 years of age. And the phenotype of that population is almost identical to this inherited population although they get their disease at a significantly later stage in life, but they too get microhemorrhages. They also get major hemorrhages, and they can also die from their stroke. So we can go from starting with a disease of a few hundred people, and if we're validated there, go to a much larger population of hundreds of thousands of patients across the world.

APP, as a target, is, of course, of interest in the Alzheimer's field as well. Now ADAD is the most genetically rich and validated subsegment of Alzheimer's as a whole. There are about 50,000-plus patients around the world. And all of these patients have APP implicated in the pathogenesis of their disease. They either have a mutation in APP that gives rise to a lot of Aß42, their deposits, they have duplications or triplications of APP through trisomy 21 or other mechanisms, where they have mutations in APP that result in abnormal proteolysis and generation of the Aß42 fragment. So there's an enormous amount of literature that points to APP as a source of pathogenic protein that drives Alzheimer's in ADAD. And so if we're thinking about validation of the Aß hypothesis in Alzheimers, the one place to think very hard about are these genetic subsets that have been identified in ADAD. And the same drug I've talked to you about for cerebral amyloid angiopathy can be applied here as well. And so the

opportunities for APP look very, very large to us, and we've begun to think very carefully about a clinical development plan, dovetailing all these multiple opportunities around APP, beginning with HCAA and ADAD, and then expanding into larger indications so that we can efficiently achieve a POC and then drive to more pivotal trials.

HCAA is an inherited mutation in the APP gene that leads to the proteolytic cleavage fragment Aß40, which is unique in the syndrome and deposits in the vessel walls in the CNS. And it does so, in particular, in the occipital lobe, where you can get these microhemorrhages. And so that bleeding phenotype usually begins in the 40s and 50s with very tiny hemorrhages in the cerebral hemisphere, particularly in the back part of the brain. But then the onset of the microhemorrhages can lead to further weakening in the vessel walls and then cause a major hemorrhage. This can lead to gradual cognitive decline, stroke and other neurologic problems in the middle of adulthood. Most people who have been affected by this syndrome die within a decade after signs and symptoms appear. It's usually fatal by the age of 60. However, there are variations depending on the severity of signs and symptoms, and some people with this disease may live longer. There are several types of HCAA, each of which have different genetic causes and symptoms. The Dutch type of HCAA is the most common form, and stroke is often the first indication of the Dutch-type HCAA, which is lethal for about 30% of people who have this condition. The mutation in the APP gene is the only known cause for Dutch-type HCAA. And as I mentioned, this is a very rare disease. Moreover, the mechanisms responsible for CAA pathogenesis, in general, and all of the downstream effects on the brain are complex and not completely understood. But it has been proposed that the amyloid is derived from neuron and it's drained along the perivascular interstitial fluid pathway of the brain parenchyma and mater meninges depositing along the vessels. In this perivascular drainage impairment sets in motion a self-reinforcing pathway by which worsening vascular amyloid accumulation leads to the activation of vascular injury pathway. And this results in the impairment of vascular physiology, leading to further increase in amyloid accumulation. This ultimately weakens the walls of the vasculature, making them prone to leaking or breaking, resulting in those micro bleeds and strokes, respectively, in the brains of these individuals. Hence, our anti-APP therapeutic approach has the potential to reduce perivascular APP-derived amyloid and HCAA, thus resulting in improved clinical outcome.

Lastly, as I just mentioned, the HCAA trial and its results has the potential to be a gateway to sporadic CAA since these 2 diseases, in patient population, have the same underlying pathophysiology.

Now let's talk about autosomal dominant Alzheimer's disease, where we can apply the same approach of RNAi-mediated silencing of APP to address the clinical symptom. The only identified deterministic factors for the development of Alzheimer's disease are the presence of inherited autosomal dominant gene mutations in 1 of 3 genes: amyloid precursor protein, presenilin-1 or presenilin-2 or duplication of APP. These mutations ultimately result in an increased production of Aß42, and approximately 50% of people from these kindreds are mutation carriers, and this is 100% penetrant. All who inherit the mutations are destined to develop dementia of Alzheimer's type generally at an earlier age, usually between the ages of 30 to 50 years. ADAD cases present with an insidious onset of episodic memory difficulties, followed by progression of cortical cognitive deficits. The most obvious differences between familial and sporadic cases of Alzheimer's disease is the younger age at onset in individuals with ADAD mutation. In vitro and in vivo studies have shown that dominant mutations frequently increase Aß42 and Aß40 deposition and alter the Aß42-Aß40 ratio. Therefore, RNAi-mediated knockdown of APP transcript in neurons may lower the production of all amyloid products, including Aß42, thus potentially halting aggregation and plaque formation. Many proposed treatments for Alzheimer's disease currently target slowing or halting of the underlying disease. Importantly, the application of Alnylam CNS platform has the potential to reduce parenchymal APP-derived amyloid in ADAD. And this may not only translate to a potential treatment in a disease where there are currently no existing disease-modifying treatments but also has the potential for expansions into sporadic Alzheimer's disease.

Our target for this program, of course, is the amyloid precursor protein, APP, which is expressed in many tissues, but more highly expressed in the nervous system. Although APP's normal function is not fully understood, it is believed to be involved in neurite growth, axiogenesis and plasticity. We do know that its complete form extends from inside of brain cells to the outsides by passing through the fatty membrane around the cell. When APP is activated to do its normal job, it is cut by other proteins into separate smaller sections that stay either inside or go outside the cell. There are several different ways APP can be cut, and under some certain circumstances, one of the pieces produced is beta amyloid. Beta amyloid is chemically stickier than other fragments produced when APP is cut. It accumulates in stages into microscopic amyloid plaques that are considered a hallmark of a brain affected by Alzheimer's disease, with pieces first formed small clustered called oligomers, then chains of clusters called fibrose and clumps the fibrose called beta sheet, and the final stage of plaque, which contain clumps of beta sheets and other substances.

According to the amyloid hypothesis, these stages of beta amyloid aggregation disrupts cell-to-cell communication and activate immune cells. These immune cells trigger inflammation, and ultimately, the brain cells are destroyed. And we should not forget about cerebral amyloid angiopathy and APP, as this disease has amyloid protein progressively depositing in cerebral blood vessel walls with subsequent degenerative vascular changes that usually result in spontaneous cerebral hemorrhages, ischemic lesions and progressive dementia.

The majority of pathogenic APP mutations cluster near the cleavage sites of the proteases' beta secretase and gamma secretase, and generally increased total Aß levels and/or Aß42-Aß40 ratio.

There were 3 mechanistic advantages of silencing APP via an RNAi therapeutic approach. The first one being the spigot versus drain. RNAi halts production of beta amyloid at its source, removing substrate required for amyloid aggregate formation. The second is intracellular versus extracellular APP targeting. RNAi is predicted to lower both intracellular and extracellular amyloid beta. And that's critically important because app intraneuronal amyloid species are thought to be contributors to disease progression.

And lastly, there is the potential for lowering of all amyloid protein species. ALN-APP is predicted to lower all APP-encoated assembly species as well as the complex Aß confirmation.

As I mentioned earlier, therapeutics based on RNAi offer a powerful method for potentially inhibiting disease targets from all molecular classes, and therefore, has the potential to be a best-in-class therapeutic approach for APP targeting. Many monoclonal antibodies against beta amyloid peptides have been tested in clinical trials for Alzheimer's disease. While several have cleared extracellular plaques, impact on disease is uncertain and likely modest. However, there are unique aspects of RNAi when you compare them to monoclonal antibodies, and some of them include things like better pharmacokinetic and pharmacodynamic profile and RNAi has the potential for greater durability. It also has the ability to target intracellular amyloid. There's also no risk of antibody accumulation around clearance sites. And lastly, an RNAi therapeutic approach has the potential to have less risk of ARIA, which is an amyloid antibody associated adverse effect.

Slide 30 highlights a nonhuman primate experiment, where animals receive a single intrathecal dose of ALN-APP. These data were first shown at a JPMorgan conference earlier this year. And as you can see on the y axis, we have the percent of protein remaining relative to baseline, while along the x axis, we of lengths of time and day. What these data demonstrate is that a single intrathecal injection suppress soluble APP alpha and beta in the CSF in a durable way after 6 months. Hence, a single intrathecal dose of ALN-APP has the potential to allow for biannual dosing or even less frequent, which would represent a huge advantage for patients.

Our plan is to file an IND for ALN-APP in mid-2021 and then initiate a Phase I clinical trial in symptomatic ADAD patients late next year. Although we will assess a variety of endpoints, including CSF and plasma biomarkers, imaging, efficacy assessments, et cetera, the primary focus of this particular clinical trial will be on safety and tolerability. There are certain key biomarkers, however, that we do intend to monitor, such as CSF APP levels as this is a proximal measure of activity. The patients we are aiming to include in this clinical trial are a group of highly motivated patients who have been pre-enrolled in a natural history study. And given the nature of their genetic disease, this population offers the appropriate benefit risk in this first-in-human trial for Alnylam, allowing appropriate assessment for safety, tolerability and dose-finding for ALN-APP.

I'll now move on to talk about our efforts developing an RNAi therapeutic targeting for the Huntington gene -- for Huntington's disease. Huntington's disease is an autosomal-dominant, gain of function genetic disease driven by a toxic mutation with a triplet repeat in the 5 prime region of this gene. It is an incurable, progressive neurodegenerative disease with devastating consequences. There is deposition of the mutant Huntington in the basal ganglia and also more broadly in the cerebral cortex. This results in progressive neurodegeneration that causes uncontrolled movements, psychiatric illness, impaired cognition and ultimately death. There are about 30,000 people affected with Huntington's disease in the U.S., and given the gain of toxic -- excuse me the gain of function toxicity of the gene, our therapeutic hypothesis is very straightforward. By knocking the gene down, this will reduce neuroma toxicity and halt progression of the disease. The overall hypothesis is that RNAi-mediated knockdown of HTT transcript in neurons will reduce both RNA-induced and protein-induced neuronal toxicity, halting disease progression. What is very interesting about this approach is that there is a potential to target the gene in different ways. And I'll touch more on that in the next slide. But this, in turn, will potentially allow for differentiation over competition via an exon 1 targeting strategy.

The pathogenesis of Huntington's disease is not fully understood. However, toxic gain of function, resulting from even Huntington, is considered the most prominent cause. This disease is caused by expansion of CAG repeats in exon 1 of the Huntington gene. So the messenger RNA gives rise to full-length Huntington, which itself is then deposited in aggregates in the basal ganglia and elsewhere in the brain. But there's an exon 1 fragment that's also yielded from the messenger RNA, and it, too, is implicated in a protein fragment that's truncated and likely takes part in the pathogenesis of this disease. Inhibiting the production of exon 1 HTT is, therefore, a clinical interest and might host a very promising strategy in treating Huntington's disease. Moreover, this raises the possibility of a differentiated approach for Huntington's disease therapy, focused on the folding or on the exon 1 fragment.

In summary, the ALN-HTT program has the potential for a best-in-class strategy with 3 key differentiating features: one being the exon 1 targeting. CAG-repeat length expands somatically throughout life, leading to increased exon 1 transcript expression. And the hypothesis is that exon 1 transcript has outsized contribution to RNA-induced toxicity and seeding of nuclear aggregates. The second is being superior delivery to striatum, as CMS-targeting ligand enables enhanced deep brain biodistribution, including knockdown in the caudate and putamen. And the third is being improved potency, duration and safety profile. Catalytic mechanism of risk-mediated RNAi can allow for greater potency and durability of knockdown in neuron. We anticipate intrathecal dosing every 6 months or even less with a best-in-class safety profile. We believe Huntington's disease is a compelling opportunity for us to be a part of, as it is a progressive neurodegenerative disease with a high-unmet medical need. And IND-enabling preclinical work is currently ongoing here at Alnylam, and we're working towards the selection of a development candidate.

What I've shared with you here is just some of our initial work in the CNS. We do have other programs and targets that we're not disclosing at this point in time. But in summary, we are extremely excited to be expanding our platform and technology into a new disease area, where we have the opportunity to develop transformative medicines for neurologic diseases. Here, we'll apply the same strategic playbook that we've used with our liver-targeting program that has proven to be a modular, highly reproducible approach to developing innovative medicines to patients in need. We plan on advancing our development candidate for ALN-APP toward the clinic with an IND filing expected in the middle of next year. And we'll plan to continue advancing 1 to 2 new CNS candidates into the clinic per year, which will complement 1 to 2 new candidates for liver-targeting programs as well.

With that, I'll now turn it back over to Vasant to moderate the Q&A session. Thank you for your time and attention.

Vasant Jadhav

Thank you, Tanya, for that wonderful presentation and Josh.

QUESTIONS AND ANSWERS

Vasant Jadhav

So we do have a number of questions coming in. (Operator Instructions) We'll begin with the questions that we have received so far. So the first one, this is about the HSD target per se. So for Josh, have we filed patents on the HSD17B13 target? Do we have freedom to operate on this that Arrowhead don't have? Could you please elaborate on this?

Joshua Brodsky - *Alnylam Pharmaceuticals, Inc. - Director of IR & Corporate Communications*

Thank you for that question. So Alnylam has filed on this target and also has vast platform IP estate on compounds of that nature. Together with the IP estate filed by our partner, Regeneron, on this target, the combined IP provides strong patent protection for ALN-HSD and the program going forward. We believe that the development and commercialization of ALN-HSD does not infringe any valid patents. And we can't comment on whether Arrowhead has freedom to operate. But we believe that we have the earliest filing for sRNA compounds targeting HSD.

Vasant Jadhav

Thank you, Josh. So I think there is another question on this one, just keeping the theme off the HSD program. So how is our Alnylam HSD program compared to the Arrowhead RNAi program also targeting the same target?

And maybe I'll take this question. So ALN-HSD is based on our most advanced siRNA design known as the ESC+ GalNAc-siRNA technology. And with this technology, we have shown improved specificity and improved therapeutic index. And we are very excited to see that with the data from HBV02 and AAT02, we are seeing favorable translation of this technology in humans. So while we don't know the exact sequence and more details about the Arrowhead sRNA. Their Phase I study appears to be similar to ours, in that, it includes NASH patients and liver biopsy to measure a knockdown. So we certainly do feel pretty good about our program.

All right. So moving on, just looking through more questions here. And maybe I'll move into the CNS space, and questions that are coming in that area. So just going through that list here. So maybe I'll begin with EPP. So -- and this will be for Tanya. So Tanya, we showed APP knockdown in CSF. What does the knockdown look like in different regions of the brain and spinal cord?

Tanya Fischer

Well, in the nonhuman primates, we see regional knockdown across the CNS anatomy. And that includes the spinal cord, the cortex, the deep brain, et cetera. And it's actually very impressive, Vasant. We're seeing 70%, 80%, 90% knockdown, depending on which exact anatomical region we're talking about in the brain and in the spinal cord. It clearly starts becoming a profile that we believe would be a leading profile and something that would be very attractive. For not just APP or Huntington's patients but generally across CNS disorders where you want an infrequently administered, safe and potent intrathecal therapeutic approach.

Vasant Jadhav

Great. Thank you, Tanya. I think another question in the CNS space, and it's more on the technology. So the question is, what's the ligand that we're using for CNS delivery and is the design ESC+ as well?

So maybe I'll take this one. So at this point, we are not providing the specifics around our conjugate directed to the CNS target. But what we can say is the siRNA design remains ESC+, the one I just talked about, the one where the improved specificity and therapeutic index. We believe this kind of technology is going to be useful across all tissues and for all of future diseases. So ESC+ design would remain. But in terms of the ligand we're not giving the specifics at this point.

Tanya, I think there was another question for you on -- while you're giving the update on the APP program, and it was more about the time lines. And the time -- the question is, what is the time line for larger opportunities following the orphan indication? I mean, obviously, this is kind of a long-term question. It might be a bit premature to give the time lines for the larger opportunities, but what are your thoughts?

Tanya Fischer

Yes. Well, as -- people that don't know me well, I like to dream big and plan big. But I think right now, we're -- here, at Alnylam, we're really focusing the opportunity and evaluating the opportunity across the full spectrum of diseases where APP plays a pathogenic role. And it's very important for us to do that. But right now, we're initially focusing on these 2 specific rare indications, the HCAA and ADAD, so that we can understand how this intrathecal delivery of the ALN-APP compound works in patients. And once we have human data, then we're going to be thinking more about the time lines for larger indications. But right now, it's a little bit premature to be thinking about specific time lines for those larger indications.

Vasant Jadhav

Right. Right. Thank you, Tanya. So maybe just going back now to HSD, a question for Josh. So Josh, what are the advantages of RNAi therapeutic targeting HSD17B13 related to other therapeutic approaches in clinical development for the treatment of NASH?

Joshua Brodsky - *Alnylam Pharmaceuticals, Inc. - Director of IR & Corporate Communications*

Well, I would say that the advantages start with the target itself because we have human genetics giving us that global natural experiment telling us that there's a cause or relationship between HSD and NASH. Other advantages extend from the platform, and that includes the safety track record, hepatocyte targeting through GalNAc, the durability of knockdown, which leads to infrequent subcu dosing, and our high degree of confidence in being able to engage the target for knockdown based on essentially a complete lack of nonresponders from a PD standpoint across the GalNAc platform.

Vasant Jadhav

Okay. Right. Thanks, Josh. Another question on HSD, a bit growing more in the data. How does the knockdown vary as a function of baseline characteristics of NHPs, including the extent of obesity and some of the parameters you've shown in the slides presented?

Joshua Brodsky - *Alnylam Pharmaceuticals, Inc. - Director of IR & Corporate Communications*

Well, we're still fully exploring -- yes, we're still fully exploring the ALN-HSD in the nonhuman primate models of the disease, but the data today tell us that we get robust and consistent target knockdown independent of the disease status in the NHPs.

Vasant Jadhav

Okay. Now -- about the other program that we talked about, and this is for the HD team, so how is Alnylam's Huntington program differentiated from the competition? What got you convinced that exon 1 approach was the right way to go? Or how did you get comfort that knocking down wild-type Huntington will be well tolerated? So finding a very important questions kind of all together, would you please elaborate on these?

Tanya Fischer

Sure. Well, based on human pathology data, it's believed that not only is Huntington's disease caused by mutant HTT from the full-length mutant transcript but toxicity is also contributed to by the exon 1 transcript. So we believe exon 1 targeting should address both aspects of the pathophysiology, providing a differentiated approach to the disease. And we know from preclinical work by us and others in human studies by Ionis and Roche, that moderate knockdown of new and wild-type HTT is well tolerated.

Vasant Jadhav

Thank you, Tanya. Tanya, I also see another question that is coming up on the remaining steps for the APP program, as you mentioned in your presentation before, you kind of gave the time lines of when we're going to go in clinic and time lines for that. The question is about what needs to be done for these things? Anything needs to be finalized? How do we -- how are you feeling about the time lines of moving with ALN-APP in clinic?

Tanya Fischer

Sure. Well, as I mentioned in my presentation, preclinical development is ongoing, and we do intend to submit the IND in mid-2021, with the Phase I trial start anticipated in late 2021. But with that said, it is safe to say that we are -- we do have a development candidate that we are hoping to be

moving into the clinic, and so we're assessing that option as we speak. And we are looking towards having current discussions with the regulatory agencies about the clinical development plan.

Vasant Jadhav

Thank you, Tanya. So just going back to HSD, and this is for Josh. So Josh, when you talk about the development for this program and the preclinical data, you mentioned that they were no toxicity of concern showed in a preclinical model. Does that imply the mild toxicity was seen, and if so, what were those symptoms?

Joshua Brodsky - *Alnylam Pharmaceuticals, Inc. - Director of IR & Corporate Communications*

So in the CTA-enabling nonclinical toxicity, there was no target ALN-HSD-related target organ toxicity in any organ in those nonclinical studies. And so for that reason, for purposes of discussing the therapeutic margin, the safety margin that I mentioned, we used the NOAL just based on the highest dose testing. There's nothing further to say because, as I mentioned, there was no drug-related target organ toxicity.

Vasant Jadhav

Right. There was nothing of concern. That means there was nothing anything mild either. We just didn't see.

Joshua Brodsky - *Alnylam Pharmaceuticals, Inc. - Director of IR & Corporate Communications*

Exactly. Nothing considered adverse.

Vasant Jadhav

Okay. All right. So in addition to the programs that we talked about, it seems like there's a question on the ALN-LEC, the ALECT2 program. So the status of this one. So maybe I'll answer this. So this program, ALN ALECT2 program remains in our list of many opportunities. We shifted the timing into 2021, and we will weigh its advancement up against other opportunities as we do for every program. As we talked about, the number of opportunities that we have in our hands, right now, I think is about 20 preclinical programs. So it will be all part of that one.

All right. Just going back and looking through additional questions as well. So I do think we have -- okay. So there's one more that is coming up. Maybe let me just read through while I translate that one. So I see there is one on the oral delivery per se. So the question is, how close to the clinic you are with the oral delivery programs?

So at this point, we're not providing any formal guidance on our oral programs. But as we reported at the R&D Day last year, 2019, we can confirm robust knockdown via oral delivery in rats as well as NHPs. And we expect a similar translation in a few months. We do see multiple opportunities for overall RNAi therapeutics going forward. But right now, we don't have any formal guidance on this one.

All right. Let's go back and see if there are any other questions that have come in. Okay, so I think there is one question, Josh, that has come in on HSD. I think we kind of asked that in terms of how would RNAi be differentiating or -- in comparison with the other molecules or other therapies. So the question specifically is, how would HSD fit in with NASH small molecule drugs? Would it ever be used in a combo? I mean, obviously, our focus is to, right now, to advance ALN-HSD, but I would like to hear your thoughts about the small molecule and combo.

Joshua Brodsky - *Alnylam Pharmaceuticals, Inc. - Director of IR & Corporate Communications*

Well, I think it's a little early to say. I think that scientifically, there was a basis to think that a combination would be beneficial. I'd say there's an openness to exploring that, but too preliminary to say anything beyond that.

Vasant Jadhav

I agree, Josh. I mean, it's too early. So with that, I think we have addressed most of the questions that we have received. So Josh, would you want to take it now and wrap up the presentation?

Joshua Brodsky - *Alnylam Pharmaceuticals, Inc. - Director of IR & Corporate Communications*

Perfect. Thanks so much, Vasant, and thanks also to Josh and Tanya for their presentations. Well, this concludes our RNAi roundtable for today, and we'll be posting the replay and slides on the Capella section of our website at alnylam.com/capella, and we'll also plan to post the transcript once that becomes available. We hope you can join us for our next RNAi Roundtable on Monday, August 10, where we'll be discussing our lumasiran program in primary hyperoxaluria type 1. Please be sure to visit Capella for all the latest on the dates and times of additional roundtables in the series.

Vasant Jadhav

Thanks, everyone.

Joshua Brodsky - *Alnylam Pharmaceuticals, Inc. - Director of IR & Corporate Communications*

Have a great day. Goodbye.
