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Alnylam Pharmaceuticals, Inc. (ALNY)

KARDIA-1 Phase 2 Zilebesiran Study Webinar

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MANAGEMENT DISCUSSION SECTION

Operator: Good day, and thank you for standing by. Welcome to the ALN-AGT RNAi Roundtable. At this time, all participants are in listen-only mode. [Operator Instructions] Please be advised that today's conference may be recorded.

I'd now like to turn the conference over to Alnylam.

Christine Regan Lindenboom

Senior Vice President, Investor Relations & Corporate Communications, Alnylam Pharmaceuticals, Inc.

Good morning, everyone. Thank you for joining us today for this RNAi roundtable where we'll be discussing zilebesiran or ALN-AGT, our investigational product in development for the treatment of hypertension. I'm Christine Lindenboom, Senior Vice President of Investor Relations and Corporate Communications at Alnylam. I'm joined today by Pushkal Garg, Chief Medical Officer at Alnylaml; Dr. Elizabeth Ofili, Professor of Medicine at the Morehouse School of Medicine; Stephen Huang, Senior Director of Clinical Research at Alnylam; and Eric Green, Senior Vice President, Development Programs at Alnylam.

In just a moment, I'll hand this over to Pushkal. But let me start with a few brief comments. Today's RNAi roundtable is a part of a series of roundtable webinars that we're hosting this summer and early fall to review progress across our various programs. Today's event is expected to run approximately 60 minutes. Pushkal will moderate the 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 this webinar and we encourage you to read our most recent SEC filings for a more complete discussion of risk factors.

And with that, I'd like to turn this over to Pushkal. Pushkal?

Pushkal Garg

Chief Medical Officer, Alnylam Pharmaceuticals, Inc.

Thank you, Christine. My name is Pushkal Garg. I'm the Chief Medical Officer at Alnylam, and I want to welcome all of you as well to this roundtable today. I may just take a couple of minutes to just give a little bit of background on Alnylam and what we've been working on for almost two decades now as a company. And that is to bring

forward an entirely new class of medicines based on the science of RNA interference. This is Nobel Prize-winning science that enables us to actually silence any gene in the genome.

Importantly, this new class of medicines has some very novel properties that allow for a potent and durable mechanism of action and a sustainable engine, product engine for innovation. As I'll show you now, this engine has actually led us to bring forward a clinical development pipeline that's composed of over 12 molecules in active clinical development. We now have four products that are marketed: ONPATTRO, GIVLAARI, OXLUMO. And as this platform has evolved, and I'll share with you in a moment, increasingly into more prevalent indications as marked by the approval in Europe and the review that's ongoing in the US for Leqvio, inclisiran, for hypercholesterolemia. Today though, we'll be talking more about zilebesiran in a few moments.

The one or two other points I wanted to bring up was that this sustainable product engine is associated with a high probability of success. This is related to the strategy that we have of pursuing genetically validated targets, programs where there are biomarkers, and looking for clear and strategic development programs that meet regulatory and commercial success criteria. And as such, we have been over 60% success rate transitioning from Phase 1 into the clinic to positive Phase 3 results.

As I just alluded to, as we've advanced this platform and the unique pharmacology of RNAi therapeutics, they are associated with particular properties that enable them to go increasingly into [ph] probable (00:03:44) indications, a very durable mechanism of action associated with clamped pharmacology, and a well-tolerated increasingly well understood safety profile, and these can enable improved access. And as I'll show you, this is particularly important and as our speakers will potentially for the treatment of diseases like hypertension.

So, turning to hypertension. We're really excited about this program, zilebesiran, as a potential way to reimagine the treatment of hypertension. Dr. Ofili will talk to you more in a few moments about the unmet need. But just a couple of points to bring up, this is an incredibly prevalent indication, 108 million people in United States, over approximately 40 million of whom are at high CV risk. The majority of patients have uncontrolled hypertension. And that poor control is exacerbated by variability in blood pressure control, lack of nighttime dipping, and poor adherence. And all of these factors contribute to the substantial risk of cardiovascular morbidity and mortality and are potentially addressable by long acting RNA therapeutics such as zilebesiran.

So, let me now turn it over to Dr. Elizabeth Ofili, who we are really, really delighted to have join us to expound more on the unmet needs for patients with hypertension. Dr. Ofili is a very distinguished Professor of Medicine Cardiologist at Morehouse School of Medicine. She is the Chief Medical Officer of the Morehouse Accountable Care Organization. She's the Chair of the Association of Black Cardiologists and has really built a national and international reputation as someone who's focused on disparities in cardiovascular health, preventative medicine, and women's health, and have been addressing that through clinical trial work, her leadership in various organizations, and also as she'll share, advancing technologies to improve cardiovascular health and reduce health disparities.

So, Dr. Ofili?

Elizabeth Ofili

Professor-Medicine, Director & Senior Associate Dean-Clinical Research Center & Clinical and Translational Research, Morehouse School of Medicine

Thank you so much, Dr. Garg. I'm delighted to be here. And so, I'll be addressing the topic of health disparities and treatment gaps in blood pressure control.

Next slide. These are my disclosures. Just want to comment that much of my research is funded by the National Institutes of Health. I do [ph] some (00:06:11) advisory board and consulting, as you see, the companies listed. And none of those will feature in my discussion today. And also, I hold the patents, and as Dr. Garg mentioned, we are looking at technologies to improve access to treatment, especially with small practices that see predominant African-American and underserved communities.

Next slide. So, these are my objectives. I want to outline the disparities in hypertension prevalence and control rates, discuss treatment gaps in hypertension, specifically the declining blood pressure control rates across all demographic groups, the multi-level barriers to treatment adherence, and the patient-centered approach to blood pressure treatment. I also want to introduce healthy Health 360x, the culturally congruent coaching for cardiovascular risk management including blood pressure control. And highlight the Association of Black Cardiologists Cardiovascular Implementation Study which is a registry that's integrating social determinants of care for underserved patients.

Next slide please. So, these are new blood pressure categories put out by several organizations including the American Heart Association, the American College of Cardiology, the [ph] EMA, and being (00:07:28) endorsed out widely. And these categories essentially redefined blood pressure, so elevated blood pressure now systolic of 120 to 129, and less than 80. We have now Stage 1 defined as 130 to 139 or 80 to 89. And the previous high blood pressure Stage 1 is now Stage 2, which is systolic of 140 or higher or diastolic of 90 or higher. And also highlighted patients that would need to immediately seek care based on blood pressures higher than 180 systolic or 120 diastolic.

Next slide please. The age-adjusted prevalence of hypertension in adults 18 and over, and I'm just using this to showcase the disparity here in terms of the prevalence of hypertension. And as you can see for both men and women, there's disparities with black hypertensives, but also overall, we can see that percentages of Americans that have high blood pressure continue to be high, averaging overall over 40%, 43%.

Next slide please. So, when we look at the treatment gaps in hypertension, as I mentioned, the 2017 ACC/AHA guidelines lowered blood pressure threshold for diagnosis of Stage 1 hypertension, as you can see those levels there, 130 to 139 systolic. This change did result in substantial increase in the prevalence of hypertension, now up to 46% across the United States adult population as I just shared. Hypertension control rates especially among non-Hispanic white adults, 55.7%, significantly higher than non-Hispanic black adults, 48%. In other words, poor control remains a problem especially for blacks, Asians, and Hispanic Americans. Non-Hispanic black adults have especially higher nocturnal blood pressures and less circadian dipping compared to their white counterparts. This is actually important overall for not just control but also for target organ damage.

Next slide please. So, when we look at this snapshot, this is looking overall at age-adjusted proportion of individuals with blood pressure control. What immediately strikes you is of course, there has now been – there was – while there was a progressive increase up until 2012-2013, there's a definite decline in control rates now. And there are a number of reasons involved in that and we will come into that discussion in a couple of slides.

Next slide please. So, when we look at adults with hypertension based on the National Health and Nutrition Survey which is a survey that's done regularly to look at the snapshot of the nation, you're comparing here 2009 to 2014 versus 2015 to 2018. So, the P values, that just shows essentially the degree of change. And what is clear is just looking at the absolute numbers, the numbers have gone up between those two time periods, higher currently for both systolic and diastolic and those are highly significant. The other thing that has increased and that's important for us when we think about what's going on with control rates, more Americans are obese. And as you can see, the percentages over 30% BMI higher now, 53.6% versus 49.6% previously. The other thing that

has changed is individuals with a usual source of care that's consistent, generally that's considered primary care providers. That number is lower in the more recent time period. And of course, diabetes prevalence is higher. So, we will come back to that in terms of our strategic approach to those individuals as we try to get better at controlling blood pressure.

This next slide now looks a little bit into more detail about the demographic breakout. And let me just share, I know it's a little bit busy, all of the sort of signals I have there, whether the asterisks or the pluses is just showing the degree of significance of the changes. But just look at it and you can see, the increase in systolic blood pressure is across the board. All demographic groups, whites, blacks, and Hispanics, much higher for blacks clearly. So is the BMI increase also across the board. And the problem with usual source of care, most dramatic for blacks and Hispanics have certainly declined again across social demographic groups. So, I think these data which were just recently published really shed some light into there are additional determinants to think about when we think about high blood pressure.

So, this next slide, we are looking at the backdrop and that's the problem of chronic diseases in America. 6 in 10 adults have chronic diseases. 4 in 10 of them have two or more of these chronic diseases. Why is that important? First of all is the trillions of dollars that are involved, $3.3 trillion in annual healthcare costs. Second of all is the important role of high blood pressure. So, when you look at five or six of these chronic diseases have a direct connection between uncontrolled blood pressure and the impact of those diseases. We're talking about heart disease, stroke, Alzheimer's disease and dementia, diabetes, and chronic kidney disease. This is why when we think about effective treatment, we also need to be looking at key lifestyle risks for chronic disease, tobacco use, poor nutrition, lack of physical activity, excessive alcohol use, all feed into poor control of high blood pressure, as well as obviously effective medications.

Next slide. I just want to frame this in terms of how I see patients in my practice. So, I just want you to meet Brenda. She's a wife, a mother of two children. She's employed full time. She commutes approximately 45 minutes, occasional travel. She has Type 2 diabetes, hypertension, and high cholesterol. She has two prescribers and has about five medications prescribed that she's supposed to take daily. And she sees with doctors on average maybe 3 times, 4 times a year maximum. Of course, she's inconsistently controlled. She has no plan for improvement. She's not activated. She's not empowered. She has inadequate knowledge despite her being a very educated woman with obviously high-powered in multiple skills. But her skills are inadequate in terms of health care, blood pressure control, and therefore, she is overwhelmed.

Next slide please. So, just look at this dosing history of two different patients. On the left and right, you are looking at patients that are recorded as having roughly 80% adherence to medications prescribed once a day. And so, this is sort of the best case scenario, if you will. And then you have the gray lines and bars of when people have skipped taking their medication. And so what you can see there is over time, while this is a sophisticated way to monitor based on who's opening that memory pillbox, it is pretty clear that there is a problem. Even when you think overall that there's adherence, there's actually inconsistency. And especially when you look at that box to the right, there's a whole week that goes by where a patient did not take their medication – that patient did not take their medication. Next slide.

And so when we think about adherence, we're looking at several categories of factors that are impacting adherence to prescription medication. So, I'm not going to go through all of these in detail, but I just want to highlight a few things because I know you have access to these slides. There are sociodemographic factors, as you see on the left-hand side, minority race-ethnicity as we just shared; social determinants, and I want to emphasize your health literacy.

Now, when we look at the health care system or the clinics, there the engagement, how are doctors and – how is the patient-clinician relationship? What's their communication style? Is it patient-centered? And does it look for cues relevant to that particular patient in terms of what they're doing with or struggling with? There's obviously these therapeutic things in the middle there that shows it matters how you – what kinds of drugs you have the patients on; how are those treatments being taken, is it once a day, is it a more complex regimen of multiple times a day. That matters.

What about individuals with multiple chronic conditions that can affect whether or not they understand the treatment, also how consistent they are. And that includes the symptom severity, multiple chronic diseases as we just shared, whether or not they're abusing alcohol, whether they have any cognitive issues, depression, dementia. Those all [indiscernible] (00:16:58).

And then what about that patient-related situation? Now, we need to be very focused on this. Sometimes, patients may not understand how effective drugs are. Sometimes, they're concerned about side effects. Sometimes, they forget to take their medicines. And then also, there's the issue of, are they following up in care and who is looking out for them? Next slide.

So, when we look at interventions, they have to be in these categories. What is happening at the physician level in terms of their ability to assess the barriers to care. Patient level in terms of how they can potentially be engaged with self-monitoring and self-management, and I'll share some examples. What about group sessions? Peer group engagements to help them. Medication treatment, it's got to be simplified. We believe single pills or combination medicines, looking at opportunity for long-acting therapy and definitely avoiding high doses and side effects. And the health system, health system can contribute because they can make it easier to have access to affordable drugs, issues of obviously beyond health systems such as co-pay, but also the health system can contribute to providing some kind of a tele-monitoring that brings the patient into care more frequently even when they're not physically in the clinic. Next slide.

So, I like this slide that was presented, and I have the reference there for you. It was really based on the broader discussion that was put out by the ACC/AHA, and this is the issue of racial disparities in hypertension. The major factors that are involved as shown in red. And these are – obviously, there's some genetic predisposition, individuals with a strong family history, but more important are some of the social determinants as I just shared.

There are the reasons for worse outcomes shown in yellow, and that's suboptimal risk stratification tools, but also variability in medication response and adherence. There are then future directions, and I believe we should pay attention to this. Novel/culturally specific treatment strategies, new therapeutic approaches that allow us to maybe dose less frequently, advancing research efforts in ethnic data collection. Next slide please.

I just want to share with you this example we have, which we're very impressed by. This is Dr. Priscilla Pemu from Morehouse School of Medicine. She was invited to the TED stage to talk about how she's been working with a platform called Health 360x. And I'll just share my disclosure. I'm involved in developing this. But this has been work that was funded by NIH, and you see there the references based on published work. This platform work with African American patients, over 500 of them now, to Morehouse School of Medicine and basically determine there are definite approaches that need to integrate cultural congruency. And she gives examples, and I encourage you to look at this TED Talk. If you just enter Priscilla Pemu, P-E-M-U, you'll have an opportunity to listen.

And the reason I bring this up is, she mentioned the fact that there's conversation underneath the conversation. Sometimes a 10-minute encounter in the doctor's office is not enough. Sometimes, coaches working with the

patients bring out new things. In this particular case, patients that have zero confidence that they can ever get blood pressure control by working with coaches, learn that it is possible. Next slide please.

So, this is the Health 360x. And just to mentioned very briefly, it is available for free to patients through some of the research that I said Morehouse has sponsored and the NIH has funded. It allows the health coach to engage with the patients. The platform can be downloaded for free on the – any of the platforms, whether it's Apple or Google Play, and you can just get more information at health360x.com. Exactly.

So, again, as I said, over 500 African Americans were rigorously tested in this clinical research study and have been promoted out there because we noticed that it is possible, as you can see in that lowest panel, to go from a baseline blood pressure – these are diabetic patients to be quite clear where they had reduced blood pressure less than 130 mm Hg by 12 weeks, and we're able to sustain it at about 130 mm Hg even after 52 weeks. The coaching stopped at the end of 12 weeks, so we know that the intervention was sustained.

And I just want to mention that the Association of Black Cardiologists is working very hard to what we call the Cardiovascular Implementation Study, which is a registry that integrates social determinants because we believe we have to do that for long-term care. And, again, we have various cardiovascular diseases that are included in the registry. But the important thing is, we are empowering small practices, looking at what's going on with their electronic medical records, making it accessible so they can use it and work with the Health 360x platform to more significantly engage their patients and consistently engage them in delivering care.

And so as I close out, I want to just thank you all for listening. I know – hopefully I didn't go through the slides very quickly. We welcome your questions. And I will turn it over now to our Chief Medical Officer – to the Chief Medical Officer, Dr. Garg.

Pushkal Garg

Chief Medical Officer, Alnylam Pharmaceuticals, Inc.

Thank you very much Dr. Ofili. We really appreciate your really great overview of the unmet needs in hypertension, particularly affecting minority and disadvantaged populations, underserved populations. I'm going to turn it over now to Dr. Stephen Huang, who's Senior Director in Clinical Research who's going to talk about the zilebesiran development program.

Stephen Huang

Senior Director-Clinical Research, Alnylam Pharmaceuticals, Inc.

Thanks, Pushkal, and thanks again to Professor Ofili for her wonderful presentation. My name is Stephen Huang. I'm a Senior Director of Clinical Research at Alnylam. And in this section, I'll present our current Phase 1 data and introduce our global Phase 2 program.

As background, this slide summarizes the therapeutic hypothesis of zilebesiran. Zilebesiran acts at the level of angiotensinogen or AGT, which is the first substrate in the renin-angiotensin system or RAS. Because AGT is the precursor of all of vasoactive angiotensin peptides and because most circulating AGT is produced in the liver, zilebesiran's hepatocyte-specific silencing of AGT is predicted to be sufficient to inhibit the systemic renin-angiotensin system and confer the therapeutic benefits of conventional RAAS blockade. This includes the lowering of blood pressure in patients with hypertension.

As shown on the right side of this slide, in contrast to conventional agents, zilebesiran has the advantage of tissue specificity for the liver, which is expected to spare local RAAS signaling in extrahepatic tissues such as the

kidney. Another important mechanistic advantage is zilebesiran's prolonged duration of action, which may achieve consistent and durable blood pressure lowering, even with infrequent dose administration. This has the potential to resolve the adherence problems inherent to daily oral antihypertensives, and to also achieve more constant for tonic blood pressure control.

The data I'll present today is from Part A of our Phase 1 first-in-human study, which explore single ascending doses of zilebesiran versus placebo given to cohorts of 12 patients. This trial is a multicenter study in the UK. And as shown on the left side of this slide, we study patients with hypertension rather than healthy volunteers to enable an assessment of therapeutic blood pressure reduction. Other than the diagnosis of hypertension, patients were selected to be healthy with exclusion criteria in place for diabetes, low GFR, or history of cardiovascular event.

As shown in the center, we've dosed seven cohorts using zilebesiran doses ranging from 10 milligrams to 800 milligrams. This corresponds to a total of 84 patients, 56 of whom have received the active drug. An unusual feature of our trial is that because it's designed to evaluate antihypertensive effects over the course of weeks or months, our key blood pressure assessments are 24-hour ambulatory blood pressure measurements or ABPMs conducted in the setting of a patient's usual activity and dietary intake.

As a Phase 1 study, our primary endpoint shown on the right side of this slide is safety and tolerability. PK and TD are secondary endpoints and change in blood pressure is analyzed as an exploratory endpoint. This study has enrolled a diverse population. As shown in this table, the median age of the study population is in the mid-50s with approximately 40% of participants being female and about a quarter of participants being black. At baseline, the median 24-hour systolic blood pressure was in the high-130s, which corresponds to the mild to moderate hypertensive range. No important differences were observed in demographic features between the active and placebo groups.

For safety, zilebesiran has been well-tolerated. Approximately three quarters of zilebesiran-treated patients have reported at least at least one adverse event. Most of these events have been mild and resolved without intervention. There have been no deaths or AEs leading to study withdrawal or treatment-related serious adverse events. No patient has required intervention for low blood pressure from excessive pharmacology. And there have been no clinically significant elevations in alanine aminotransferase, serum creatinine, or serum potassium. Minority of patients have reported injection site reactions. All these were mild events that resolved in one to two days.

Pharmacodynamic data show dose-dependent and durable reductions of circulating angiotensinogen after single doses of zilebesiran. After doses of 100 milligrams or higher, reductions greater than 90% were achieved by week 3 and persisted through the end of the protocol's 12-week treatment period. The greatest reductions in serum AGT were observed in the 800-milligram group where all patients achieved more than 95% lowering. After the 12-week treatment period, our protocol requires patients to return for safety follow-up every three months until their serum AGT recovers. Data from these visits show meaningful AGT knockdown up to 24 weeks after higher doses, further supporting that infrequent dosing will be possible.

These reductions in serum AGT were accompanied by corresponding clinically significant reductions in blood pressure. The graph on the left shows change from baseline in blood pressure assessed by a 24-hour ABPM performed at eight weeks after single-dose administration. After doses of 100 milligrams or higher, mean reductions in 24-hour systolic blood pressure greater than 10 millimeters of mercury were observed, but the mean reduction of 17 millimeters of mercury in the 800-milligram group. Once we observed these positive results, we amended the protocol to perform an additional ABPM at the end of the 12-week treatment period. And as

predicted from the serum AGT data, this confirm persistent antihypertensive effect through week 12, illustrated in the graph on the right.

Looking at individual patient responses, this slide shows a waterfall plot comparing the individual responses of all patients who received placebo shown here in blue to the responses observed in the pooled group of all patients who received a zilebesiran dose of 100 milligrams or higher shown here in red. Even eight weeks after dosing, clear differences in the change from baseline in 24-hour blood pressure are evident between the groups. As shown on the right, the majority of active patients responded with zilebesiran with a median treatment effect of approximately 10 millimeters of mercury.

If we then explore in the concept of constant 24-hour blood pressure control, this slide shows the mean 24-hour blood pressure profile of all patients in the Phase 1 who received a single dose of 800 milligrams of zilebesiran, shown here in blue, versus those who received placebo, shown here in red. Consistent with constant or chronic antihypertensive effect from zilebesiran, blood pressure is reduced relative to placebo at every hour of the day and nighttime periods.

The planned potential dosing regimen data from the single ascending dose study have been used to generate clinical pharmacology modeling. As illustrated here, the model predicts the potential for both quarterly and biannual dosing regimen, showing that reductions in systolic blood pressure greater than 10 millimeters of mercury can be maintained throughout these dosing intervals.

In the remaining slides, I'll summarize the current status of our ongoing Phase 1 study, and then introduce our plans for Phase 2. Starting with Phase 1, dosing in the single ascending dose study I just presented is now complete. Given the long-term knockdown of serum AGT, safety follow-up of individual patients will continue, and we anticipate sharing updated data from these assessments later this year. The Phase 1 has two-part study design to assess the tolerability of zilebesiran during potential augmented pharmacology, induced either by a low salt diet or by co-administration of the conventional RAAS inhibitor, irbesartan. These cohorts have completed dosing with data readout expected later this year.

Finally, a Phase 1 multidose cohort in obese patients to assess the effect of repeat dosing and the potential impact of body weight on PK and PD is currently enrolling with the goal of completion by the year's end.

Moving to Phase 2 clinical development, two global studies are planned in KARDIA-1 and KARDIA-2. KARDIA-1 is designed to evaluate the efficacy and safety of zilebesiran as a monotherapy. I'll describe the study in more detail in the next slide. Our IND opened in May with study initiation earlier this month. KARDIA-2 is designed to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients with hypertension despite treatment with a potent RAAS inhibitor, a calcium channel blocker, or a diuretic. We are targeting study initiation in late 2021.

Looking at the KARDIA-1 trial in more detail, it's designed as a randomized, double-blind, placebo-controlled, dose-ranging study. As shown on the left, compared to Phase 1, the Phase 2 population has been expanded to include individuals up to 75 years of age and those with diabetes or GFR as low as 30. After a washout period, patients will be equally randomized to placebo or to four active regimens of zilebesiran, evaluating both quarterly and biannual dosing regimens. The primary endpoint is changed from baseline in systolic blood pressure at month 3, which corresponds to the end of a strict placebo-controlled period. Additional blood pressure assessments including at month 6 are secondary endpoints.

As in the Phase 1, ABPM will be used to evaluate the consistency of blood pressure control over the 24-hour period. In addition, repeated blood pressure assessments by both ABPM and office measurements will be collected to evaluate the consistency of blood pressure control over the entire multi-month intra-dosing period. We're excited to share that we've activated our first site, and that the KARDIA-1 trial is now open.

In summary, single doses of zilebesiran have been well-tolerated in Phase 1. Doses of 100 milligrams or more achieved more than 90% reductions in serum AGT, and more than 10 millimeters of mercury reduction in systolic blood pressure. These data supports the potential for infrequent quarterly or biannual dosing regimens, which will be evaluated in Phase 2. The Phase 2 KARDIA-1 trial is now open, and we're looking forward to opening the KARDIA-2 trial later this year.

Now I'm happy to hand the presentation over to Eric.

Eric Green

Senior Vice President-Development Programs, Alnylam Pharmaceuticals, Inc.

Thank you, Stephen. Hello, everyone. I'm Eric Green, Head of Development Programs here at Alnylam. Today, I'll provide a brief view of the commercial opportunity we see for zilebesiran as a potential treatment for patients with hypertension. Based on the data that we have just reviewed, we believe we have the opportunity to reimagine the management of hypertension, a highly prevalent disease that has been devoid of significant innovation for decades.

Dr. Ofili already spoke to some of the challenges of adherence, especially for the treatment of chronic diseases that are generally asymptomatic. On the left, here's another depiction of the various barriers between a prescription being written and a patient taking their medication correctly and for an extended period of time. Though these data are not specific to hypertension medications, the general trend would obviously hold. Several of the potential features of zilebesiran such as the infrequent dosing and ability to reduce the daily pill burden could help improve patient adherence. The final bullet focusing on tonic blood pressure control over the dosing period, for example, three or six months, is a good segue to the next slide.

In this framework by Kario et al, there are three components to 24-hour blood pressure control: the 24-hour blood pressure level, nocturnal blood pressure dipping, and blood pressure variability; such as the morning BP surge. The quantity of BP reduction is important. For example, lowering blood pressure by 10 millimeters to 15 millimeters of mercury. But ideally, that reduction is consistently maintained throughout the 24-hour period and doesn't wane during the night; the challenge with some oral medications that have peak to trough effects every day. Restoring normal nocturnal dipping and avoiding exaggerating morning blood pressure surges are more qualitative aspects for blood pressure control, but also have an impact on CBD risk.

Achieving all three of these objectives could reduce the risk of organ damage and cardiovascular disease events. Given zilebesiran's profile of potential features, we may have a positive impact on each of these three areas. We look forward to seeing additional data from the KARDIA studies to further understand the profile of this product.

When considering the future commercial populations for zilebesiran, we are considering two patient segments, assuming a successful clinical development and ultimately regulatory approvals. The first segment includes patients with uncontrolled blood pressure at high risk for major adverse cardiovascular events. We have estimated the US prevalence of this population to be approximately 38 million people, of which approximately half have uncontrolled blood pressure despite treatment with currently available therapies.

The population is defined as patients with a cardiovascular risk or a previous medical history of a cardiovascular event. The current treatment landscape in this therapeutic area is dictated by well-established treatment guidelines with different classes of medicines being prescribed based on hypertension severity, specific comorbidities that that patient may have. As many of these patients are taking medications to address their multiple comorbidities as Dr. Ofili pointed out earlier, an example is Brenda. Daily pill burden can be significant, and medication adherence is often suboptimal; also, as you heard earlier.

Lack of adherence is of utmost concern to these patients at high risk for cardiovascular events where uncontrolled blood pressure can lead to poor clinical outcomes, and antihypertensive medication with tonic blood pressure control and infrequent dosing could be advantageous in treating this population. The disease burden of hypertension is significant. Uncontrolled hypertension is a major risk factor for cardiovascular disease and morbidity and mortality. And annually, approximately 1.5 million people in the US suffer from myocardial infarction and stroke with approximately half of these major adverse events attributed to hypertension.

The burden of hypertension and health care costs is also quite significant. Annual direct and indirect costs of hypertensive disease and stroke is estimated to be approximately $55 billion and $45 billion, respectively. While only approximately half of these stroke costs are attributed to hypertension, additional health care costs are also incurred due to hypertension within the broad category of heart disease. Given the unmet medical need for treatments that provide further blood pressure reduction that is durable and less variable in patients at high risk for major adverse CV events, we estimate zilebesiran could achieve revenues of greater than $4 billion a year at peak.

The market for broad hypertension treatment is also significant. As Pushkal mentioned earlier, over 100 million patients in the US have hypertension. And despite availability of multiple classes of antihypertensive medications, approximately three-quarters of these hypertensive patients do not achieve the controlled blood pressure. The general treatment paradigm and disease burden is the same as described on the high CV risk population on the previous slide.

However, given the endemic adherence issues associated with uncontrolled blood pressure and primary hypertension, zilebesiran has the potential to be a foundational antihypertensive medication that would be infrequently administered and provide sustained and durable blood pressure lowering in patients that have difficulty in achieving their blood pressure goals. Given this, we believe that the treatment of primary hypertension could also be a $4 billion market opportunity at peak. Of course, these two populations do have some overlap, so the commercial potential isn't necessarily additive.

Then to summarize, we are quite excited about the continued development of zilebesiran as a potential treatment for patients with hypertension. We believe there remains a significant unmet need in this disease, particularly in patients with uncontrolled blood pressure at high risk for cardiovascular events or even potentially in patients with primary hypertension. The initial Phase 1 data are encouraging, demonstrating meaningful blood pressure reductions at higher zilebesiran doses and robust pharmacodynamic effect, showing durable reductions of serum AGT that supports the potential for quarterly or even biannual dosing. And with the initiation of the cardio clinical development program, we are moving into the next important phase of this program.

And now I'll turn it back to Pushkal to moderate the Q&A session. And as a reminder, please submit your questions by clicking the Ask A Question button or field on the Web chat. Pushkal?

QUESTION AND ANSWER SECTION

Pushkal Garg
Chief Medical Officer, Alnylam Pharmaceuticals, Inc.
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Thank you, Eric. Thanks, Stephen. Thanks again to Dr. Ofili for all of your great presentations. And as Eric said, we're now going to open up for question-and-answer. And if you do have questions, please enter them into the webinar portal.

So, the first question that came in is just – is for Dr. Ofili. So, Stephen reported about 10 millimeters to 15 millimeters of systolic blood pressure lowering with zilebesiran. Dr. Ofili, can you just comment on what is considered a clinically meaningful reduction in blood pressure, systolic or diastolic? How do you think about that?

Elizabeth Ofili
Professor-Medicine, Director & Senior Associate Dean-Clinical Research Center & Clinical and Translational Research, Morehouse School of Medicine
A

Right. In general – thank you so much for the question. In general, when we look at single-drug therapy, obviously, reductions of 5-millimeter is considered important. And then when we add combination therapies, we may get more, but usually between 5-millimeter and 7-millimeter reduction. Most antihypertensive agents are in that range.

Pushkal Garg
Chief Medical Officer, Alnylam Pharmaceuticals, Inc.
A

Thank you, Dr. Ofili. Stephen, a question came in around a concept on the study diagrams for KARDIA-1 and KARDIA-2 where you've talked about time-adjusted average blood pressure. And some questions about, what does that exactly mean? How do you look at that? And why is it important?

Stephen Huang
Senior Director-Clinical Research, Alnylam Pharmaceuticals, Inc.
A

Thanks, Pushkal. So, this refers to the time-weighted average of multiple blood pressure measurements collected over time, which can be calculated as an indicator of overall blood pressure control over an extended period. And we include this as an endpoint in our trials to study the concept of durable and constant antihypertensive effect for weeks or months after dose administration, which we see as a potential novel feature of zilebesiran.

Pushkal Garg
Chief Medical Officer, Alnylam Pharmaceuticals, Inc.
A

Interesting. So, then this actually I think may link to some other questions that have come in which is, you presented these 24-hour plots of blood pressure. Why does the blood – we talked about clamped pharmacology. Why does the blood pressure go up and down then over a 24-hour period? Is that the AGT reduction is changing, or what does that represent?

Stephen Huang
Senior Director-Clinical Research, Alnylam Pharmaceuticals, Inc.
A

Sure, Pushkal. I'll start with the comment about change from day to night. So, reduction of blood pressure at nighttime relative to daytime is a normal physiologic pattern called dipping. That's observed in healthy individuals without hypertension. So, even with optimal pharmacology, the goal of optimal 24-hour blood pressure control

includes the restoration of this normal circadian pattern. And we've all in fact assessed the restoration of dipping in our Phase 2 trials.

If you'd like me to comment on the 24-hour blood pressure profile, the profile of zilebesiran we showed indicates reduced blood pressure relative to placebo at every hour of the day and nighttime periods. In contrast of this, some commonly used oral antihypertensives that are short-lived and administered once-daily have reduced efficacy towards the end of their 24-hour dosing interval. This can manifest as reduced separation from placebo on that type of 24-hour blood pressure profile.

Depending on the timing of administration, which can be variable as shown by Dr. Ofili's presentation, this reduction of controlled but short-lived oral antihypertensives can lead to nocturnal hypertension or to an exaggerated morning blood pressure surge.

Pushkal Garg
Chief Medical Officer, Alnylam Pharmaceuticals, Inc.

A

So, just to follow up, are you suggesting that if you took – if you look at that same profile for conventional agents, that gap between placebo and active would actually be fluctuating more over time is what you would expect to see based on the pharmacology?

Stephen Huang
Senior Director-Clinical Research, Alnylam Pharmaceuticals, Inc.

A

That's correct.

Pushkal Garg
Chief Medical Officer, Alnylam Pharmaceuticals, Inc.

A

Interesting. All right. Dr. Ofili, there was a number of questions and interest in some of the work that you presented around adherence. You presented a narrative of a patient named Brenda. But I think one of the questions that came up is, it seems that a number of patients fill prescriptions, but then they stop taking them over time. Can you expand a little bit more on what are some of the common reasons that people stop taking medicines over time after they're initially prescribed?

Elizabeth Ofili
Professor-Medicine, Director & Senior Associate Dean-Clinical Research Center & Clinical and Translational Research, Morehouse School of Medicine

A

Yeah, so thank you again for that question. So, what we find is that sometimes, the most common reason is patients may have a side effect or what they consider to be a side effect, right. Remember, many patients with high blood pressure do not have just one condition. So, they've got different medicines they're taking, and sometimes, they think they have a side effect, at least, what my patients tell me, sometimes they stop everything. And I have to really get into discussion with them that that is really not – there are some side effects that we can anticipate. So, you can address that upfront by sharing some potential side effects with them. But I do believe that one of the biggest difficulties patients have is that they now have all these multiple medications, their regimens are complex, there's polypharmacy.

[indiscernible] (00:46:52) Brenda has only two conditions as you saw. She already has four prescribers and she's probably taking five or six including stuff that she's taking over-the-counter. And so, I think the more we can simplify and then couple that with clear education upfront about what patients can expect, and then especially for high blood pressure, for patients with high risk cardiovascular disease, they cannot stop taking their medicines without risking a rebound and then potentially problems with cardiovascular exacerbation. I just had a patient

yesterday in my office where she thought, she said, I'm confused. I think I'm not taking my medicines correctly. [ph] She's like (00:47:41) I usually start in the morning and I finish taking everything by 2 or 3 in the afternoon. So, you see patients just think, if I take all five right at once, I'm going to get sick.

So, again, that requires education. And patients need to know that some of the medicines because you take them don't mean that you'll have magnified side effects. And then there are things where they need to know [ph] if you need to (00:48:06) shift this to bedtime. So, those kinds of communication are important before we outright just dismiss a patient that's just not wanting to take the medication.

Pushkal Garg
Chief Medical Officer, Alnylam Pharmaceuticals, Inc.
A

That's really helpful context. Maybe just building on that, what are some of the tactics that you've employed? You talked about some technology solutions that you're involved and your colleagues are involved in developing. But specifically in terms of talking to patients about adherence, are there specific tactics that you pursued or employed that you find helpful?

Elizabeth Ofili
Professor-Medicine, Director & Senior Associate Dean-Clinical Research Center & Clinical and Translational Research, Morehouse School of Medicine
A

Yeah, I really and I appreciate that question because it speaks to what I deal with every day with my patients. Patients actually obviously want to get better that's why they came. But they don't know what they don't know. And what I try to explain to my patients is you're not alone. Over 85% of Americans do not have appropriate health literacy. And as defined by the National Academy of Medicine, that means you can't – the patients that have low health literacy do not have the ability to comprehend instructions that are provided whether it's at the pharmacy or the doctor's office and act on it in a consistent manner for the benefit of their health. So, when we start with that premise and make everybody comfortable and say, this is not saying you are ignorant. Health literacy is not about ignorance. Health literacy is about understanding how things potentially interact with your disease condition, with your own makeup, and how that could lead to better outcome depending on how you take the therapy.

So, once we clear that hurdle, then I say to them, the next thing is what's going on inside your body, how are you detecting that. Don't assume that you're going to have a headache when your blood pressure is elevated, because by the time you get the headache, you're probably about ready to have a stroke which means you should be in an emergency room. So, I explained to them that there is no substitute for tracking your own health. It is your activity. It is what you put in your mouth. It is the actual blood pressure that you're measuring and now we have all these technologies. But people get confused what should I follow, what about my sleep. And I explain that sleep actually also has relevance, but it is about how well and the quality of your sleep. So, before you get all carried away with all of the devices, focus on your blood pressure. And then I show them example of me and I say, look, this is what happens. This is how my blood pressure varies and I don't have high blood pressure, but it's varying [indiscernible] (00:50:51) but sometimes, it goes into an elevated rate. So, you need to know that.

And that for me, when I don't have enough sleep or when I'm not as active, when I eat a certain diet, it affects that. So, when people know that about themselves especially with patients that are hypertensive, whether this variation is really more marked and more prominent as you heard from the discussion, and I think they then integrate that into their behavior. The most excited patients I have are patients who come back and say, oh my goodness, look what happened. I took my medicine, blood pressure didn't drop like I thought it would, but it was in a good range. But even when I went for a walk and came back, I saw the change in my blood pressure. So, just understanding these ranges but also bringing them into the discussion about what a pathologic variation versus something that they can expect so they don't freak out.

So that kind of – it's an ongoing process. And that's why for us, we also bring in our team approach where we bring in coaches because the doctor only has, whatever, 10, 15 minutes with the patient the way our health system is designed and most patients are spending the majority of their time going about in the community. So having that help just gets them more comfortable, more confident in their ability to help manage their own health.

Pushkal Garg
Chief Medical Officer, Alnylam Pharmaceuticals, Inc.
A

That's really elucidating, Dr. Ofili. I think you've highlighted what I think many people may take for granted as being somewhat simple with all the medicines that are available, but really, it is a very complex milieu that you have to negotiate with patients and health systems, et cetera. So, that's really helpful. Just one other question came through. Does telehealth play a role? What you've described, it really highlights perhaps a lot of touch points with patients and frequent check-ins has – how does telehealth play a role in any of this?

Elizabeth Ofili
Professor-Medicine, Director & Senior Associate Dean-Clinical Research Center & Clinical and Translational Research, Morehouse School of Medicine
A

Again, excellent question. So, what we found and this was actually a revealing moment during the pandemic because people were not going to the hospitals, they were not coming to the doctors, were having more heart attacks and strokes. And so, when the reimbursement allowed us to deal with telehealth, the stuff just went through the roof. Now, what happened with us, because we already had this platform, we basically told patients – because some patients, their technology doesn't allow them to get into video conference. We told them, that's not the key thing. The key thing is what have you monitored that you can share with us, right. So, then patients were able to – in our model, they can just – we connect with them once they have the platform through a link.

And they just then – they don't need to do anything other than enter their data into the platform and then we get to communicate because they say they give us permission as their doctor or coach to have this communication. So, it kind of gives them that sense of security. Hey, that, okay, my doctor is looking at this, and if it's in the dangerous zone, they'll tell me what to do. And then that is our classification. We call it telemonitoring and telehealth because it's not just about just going in and doing something. It's responding to something that the patients collected essentially and sent in.

And so, that has really been very, very helpful and it's not as – the numbers are not as high as when we were in the middle of the pandemic. But then there are many practices that now want to do this in an ongoing manner for patients especially those that have multiple comorbidities, helps to control blood pressure. They're not going to be coming into the office every month or every week. So, we just then use this as a way to get that blood pressure controlled. And also, when we change medications because you kind of want to know and that gives patient's confidence that, okay, I can take that new medicine because somebody is watching, somebody is monitoring what's going on with me.

Pushkal Garg
Chief Medical Officer, Alnylam Pharmaceuticals, Inc.
A

That's really helpful to hear. It's wonderful. There's advances in this space that actually that's [ph] brought on (00:55:21) by the pandemic, so maybe [ph] it's (00:55:23) one positive outcome there.

A number of questions that have come, maybe Stephen and Eric, for you two around therapeutic positioning, [ph] co-zilebesiran (00:55:33). Will it be used as a first line therapy? Will it be used as add-on therapy? Will it be used in treatment-resistant patients and will there be studies in that population? And then likewise, Eric, what might be

the payer sort of requirements? Will there be [indiscernible] (00:55:51), et cetera. And so do you see [indiscernible] (00:55:52) as a first line agent or a later line agent? What's our thinking around those topics?

Eric Green
Senior Vice President-Development Programs, Alnylam Pharmaceuticals, Inc.

A

We'll let Stephen start on design of our KARDIA studies and the data we're starting to generate to help inform some of those answers.

Stephen Huang
Senior Director-Clinical Research, Alnylam Pharmaceuticals, Inc.

A

Sure. So, thank you, Eric. So, our initial thinking for positioning focused on patients with unmet need with current therapies including patients with resistant hypertension, patients with high cardiovascular risk who are unable to achieve adequate control despite treatment with multiple conventional anti-hypertensives. So, we are developing trials like KARDIA-2 to understand how our drugs could combine the conventional agents in those sorts of populations. However, as we've seen the data develop from Phase 1, observed the very constant and durable control of blood pressure, and as we've learned from experts like what Dr. Ofili taught us about how adherence challenges exist at all stages of disease, we've actually also started to think about the possibility of being used earlier in the treatment paradigm possibly at the foundational therapy.

Eric Green
Senior Vice President-Development Programs, Alnylam Pharmaceuticals, Inc.

A

Great. And once we've learned more obviously from our two Phase 2 studies, we'll then inform our development of our pivotal Phase 3 studies, all of which data will inform which patient population may benefit most initially and then over time as we continue development. So, we highlighted two potential populations in the slides. Those patients at high CV risk [indiscernible] (00:57:26) prior event or have prognostic factors indicated they may be at high risk, could be a very appropriate patient population, the first use of zilebesiran.

As far as what health payers and governments may think about this, this is a huge healthcare burden. The treatment of hypertension or lack of control of the hypertension is a huge cost. We believe with an innovative profile like zilebesiran, hopefully, we'll continue to generate, we have the chance to change health at a population level and lower that catastrophic risk across the entire population whether it's government, a region, or even a particular commercial payer.

We do recognize that as we address a much more prevalent population, price will be aligned with other innovative drugs in a very prevalent population. And we will build on our history over the last number of years of being innovative in our pricing and our interactions with payers and with governments and in value-based agreements that we really hope that we will be able to make zilebesiran available broadly for patients that may benefit.

Pushkal Garg
Chief Medical Officer, Alnylam Pharmaceuticals, Inc.

A

Very, very helpful. Thank you, both. I think we have time for one last question. So, there were a couple questions that I'll sort of bundle together, Stephen, maybe you're in the best position to answer which is around the emerging safety profile of this mechanism. One was, have we seen episodes of hypotension in the Phase 1 study? Can you lower [ph] AGT (00:58:56) too much? And then, do we expect with this RNAi approach that we would see other common side effects that are associated, for example, with ACE inhibitors, whether it be renal safety concerns or angioedema? Can you just comment on a couple of those things?

Stephen Huang

Senior Director-Clinical Research, Alnylam Pharmaceuticals, Inc.

A

Sure, Pushkal. So, the possibility of hypotension from excessive pharmacology is something that's important. And we tried to gain early insight from that – into that with animal models. So, in those preclinical models, deep knockdown of circulating [ph] AGT (00:59:34) even in normotensive animals was not associated with hypotension. Our trials monitored carefully for low blood pressure. And as I mentioned in our presentation, no patient in the Phase 1 study has developed a hypotensive event even at the highest doses.

We'll continue to monitor carefully going forward for low blood pressure. But it's worth noting that we have also conducted preclinical experiments to confirm that standard treatments for low blood pressure such as increasing dietary salt intake and use of common [indiscernible] (01:00:07) agents or [ph] may affected (01:00:09) individuals who have been treated with zilebesiran.

For the other types of renal safety events associated with conventional RAAS blockers, here, our future tissue specificity is important. So, with our approach of renal sparing, we only target liver angiotensinogen. And that's notable because there are data to indicate that one of the reasons patients who are treated with conventional ACE inhibitors or ARBs may experience liver toxicity is due to the local effects of those drugs in the kidney. So, we view zilebesiran's ability to just target liver-specific angiotensinogen without impacting the kidney to be a novel opportunity to potentially avoid the renal injury that's associated with conventional drugs.

Pushkal Garg

Chief Medical Officer, Alnylam Pharmaceuticals, Inc.

Very helpful, Stephen. Thank you. I think that's all we have time for in terms of questions today. I'm going to turnover to Christine. But I just want to thank all of our presenters and thank all the participants who dialed in and asked questions. And we look forward to giving you more updates on zilebesiran in the coming months. Christine?

Christine Regan Lindenboom

Senior Vice President, Investor Relations & Corporate Communications, Alnylam Pharmaceuticals, Inc.

Thanks, Pushkal. And thank you to Dr. Ofili, Stephen, and Eric as well. So, this will conclude our RNAi roundtable for today. We'll be posting the replay and the slides on the Capella section of our website at alnylam.com/capella. And we'll also plan to post a transcript once that becomes available. We hope you could join us for our next RNAi roundtable on July 16 where we'll be discussing patisiran and vutrisiran in the development for ATTR amyloidosis.

Thank you, everyone, and have a great day. Goodbye.

Operator: Thank you. Bye-bye.