Alnylam Pharmaceuticals Inc "RNAi Roundtable" Webcast Series: ALN-AGT, in Development for the Treatment of Hypertension

Cambridge Jun 24, 2020 (Thomson StreetEvents) -- Edited Transcript of Alnylam Pharmaceuticals Inc conference call or presentation Tuesday, June 23, 2020 at 6:30:00pm GMT

CORPORATE PARTICIPANTS

Jae B. Kim

John M. Maraganore, Alnylam Pharmaceuticals, Inc. - CEO & Executive Director

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

Lauren Melton

CONFERENCE CALL PARTICIPANTS

Akshay Desai

PRESENTATION

Operator

Good day, and welcome to the Alnylam Pharmaceuticals Roundtable Conference Call. Today's conference is being recorded. At this time, I would like to turn the call over to Josh Brodsky. Please go ahead.

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

Good afternoon, everyone. Thank you for joining me for today's RNAi Roundtable, where we'll be discussing ALN-AGT, an RNAi therapeutic in development for the treatment at hypertension. I'm Josh Brodsky, Director of Investor Relations and Corporate Communications at Alnylam. With me today on the line are John Maraganore, Alnylam's Chief Executive Officer; Jae Kim, Vice President of Clinical Development; Lauren Melton, Senior Director and Program Leader for ALN-AGT; and Dr. Akshay Desai, Director of the Cardiomyopathy and Heart Failure Program in the Cardiovascular Division at Brigham and Women's Hospital and Associate Professor of Medicine at Harvard Medical School.

Today's RNAi Roundtable is the first in a series of roundtable webinars that we'll be hosting over the coming weeks and months to review progress across our various programs. Today's event is expected to run between 60 and 75 minutes. John will moderate the Q&A session at the conclusion of the presentation. (Operator Instructions)

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 so with that, I'll now turn it over to John.

John M. Maraganore, Alnylam Pharmaceuticals, Inc. - CEO & Executive Director

Thanks, Josh. This is obviously the first RNAi Roundtable event for this current year, but it's the seventh annual roundtable series that we've done. And it's really amazing to see the progress of RNAi therapeutics over the last 7 years. And of course, this is just the beginning.

RNAi is the new -- next slide, please. RNAi is a new class of medicine. It's a powerful approach to treat human disease. We're really excited about the transformational impact that we've seen with many of these products that we've advanced into clinical development, and we're proud at Alnylam to have pioneered this whole new frontier of medicine.

Next slide, please. Now at Alnylam, we have built industry-leading pipeline with 11, and soon 12 programs in clinical development, including 5 that are in late-stage development, with 2 programs that are currently in registration. These late-stage programs are obviously positioned to fuel continued growth for Alnylam in the next few years, helping us build a [top 5 biotech] company.

Next slide, please. On this slide, you can see our early- to mid-stage pipeline, which, of course, has 5 programs that are currently in Phase I and Phase II development, and importantly, a product engine that is capable of generating 2 to 4 new INDs per year for sustainable innovation. So very excited about where these programs are going.

Next slide, please. Now of course, today, we're focused on ALN-AGT, which really speaks to the opportunity for RNAi therapeutics to transform the treatment of chronic prevalent diseases affecting millions of people around the world. And this is why ALN-AGT is such an important program in our pipeline. You'll hear more about the unmet need from Dr. Desai in just a minute, but it's clear that hypertension is a massive public health issue where innovation has been lacking for decades and where it's desperately needed. We believe that RNAi therapeutic that provides consistent and

tonic blood pressure control could be a major breakthrough for the treatment of hypertension with meaningful impact on downstream clinical sequela such as strokes, heart attacks and kidney failure.

So with that, let me now turn the call over to Dr. Desai. Dr. Desai?

Akshay Desai,

Thanks very much, John. It's a pleasure to be here, and to talk -- and my role is to really give you a bit of background about the problem of hypertension and some of the gaps that exist in our current therapeutic armamentarium. If we move then to the next slide, which has the objectives. I wanted to really highlight some of the basic epidemiology of hypertension to give you a context as well as the apparent graded and continuous association between blood pressure and cardiovascular risk.

I'm going to talk a little bit about how our definitions and clinical practice of hypertension has evolved in relation to that data, and then really close with some discussion of the therapeutic gaps which may be relevant as we consider the positioning of ALN-AGT in therapeutic arsenal moving forward.

So if we move to the next slide, I don't need to tell anyone who's engaged in this space that hypertension is an important and a treatable risk factor for cardiovascular disease. The risks are also important with regard to end-stage renal disease, which hypertension contribute to a large scale. Hypertension may be less appreciated though as the leading cause of disability-adjusted life years worldwide and then there's more from death and disability related to hypertension than any other single risk factor that we encountered in day-to-day practice in cardiology. And suboptimal blood pressure control is really most common attributable risk factor for cardiovascular disease and cerebrovascular disease, and by that I mean stroke, myocardial infarction and it's the leading cause of chronic kidney disease progression. So a huge amount of morbidity and mortality attributable to hypertension.

If we move to the next slide. This is a schematic of disability-adjusted life years and this concept really of the DALY is really, meaning that this is equivalent to 1 year of healthy life lost. So the more disability-adjusted life years, the more morbidity associated with the disorder. And this is a histogram of the disability-adjusted life years attributable to each blood pressure on the X-axis. I think what's important here is that there are protean consequences of hypertension including ischemic heart disease which is the predominant manifestation. Hemorrhagic stroke is a bit more common, then ischemic stroke as a consequence of hypertension. Chronic kidney disease is next and then there are a range of other sort of causes, various problems that happen.

When I think of sometimes, there are also discussion in hypertension where people have historically cut -- set the cut point for therapy at about 140 over 90, is that a large proportion of disability and death associated with hypertension happens in patients in what we used to call normal blood pressure with blood pressures between 150 -- 115 and 140 millimeters of mercury systolic. You can see here that about 1/3 of the disability-adjusted life years attributed to hypertension happen in that lower end of the bell curve. And this is really early data that has kind of pushed us to rethink our approach to hypertension and how aggressive we ought to be.

Next slide. This is older data, largely initially for framing (inaudible) but it's been validated in a large number of epidemiologic context, highlighting the graded and continuous relationship between both systolic and diastolic blood pressure and cardiovascular risk. And you could draw these same curves for any cardiac outcome including ischemic heart disease, heart failure, fatal and nonfatal stroke. And I think what's important to look at in these lines is that relationships persist down to blood pressures of 115 over 75 millimeters of mercury, which is the truly nadir of normal blood pressure of when we're examining this topic. There is absolutely no variation in this pattern by ethnicity or gender. And so this is a ubiquitous association and really conditions now our evolving approach to management of hypertension in practice.

The next slide. This is a cartoon that really takes data from that same previous analysis. And now it shows you one of the effects on cardiovascular risk would and this is just cardiovascular death, as an example. For each 20- over 10-millimeter increment in blood pressure is because there is a doubling for each 20- over 10-millimeter increment in blood pressure, that's systolic over diastolic of risk. You can see that by the time you get to pressures of 175 over 105 compared to somebody with truly normal blood pressure of 115 over 75, the risk is amplified. That's nearly a full. And so there's a huge value to blood pressure reduction even at the lower end of the range.

The next slide really defines the response of the risk that we observed to antihypertensive therapy. This is a meta-regression of 123 studies, enrolling over 0.5 million patients. Each bubble on the graph represents a single study. Larger bubbles are larger studies. The overall observation that there is a tight relationship between the degree of achieved blood pressure reduction and the degree of reduction in cardiovascular event. And that reduction persists all the way out to -- with the greatest reductions observed in higher -- in the trials that observed the highest reductions in blood pressure.

What's interesting about this data is that it is independent largely of the therapy employed. I'll talk a little bit about therapy later. But in general, it's the amount blood pressure reduction achieved rather than the specific therapy used to achieve it that seems to drive most of the risk reduction.

If you look at the right-hand side of the slide, you can see the attributable reduction in risk for each 10-millimeter reduction in blood pressure in cardiovascular events, ischemic heart disease, stroke, heart failure, renal failure and the all-cause mortality. You can see that every 10-millimeter reduction has potent effects on long-term cardiovascular risk. And these reductions are pretty consistent across different morbidities, for example, diabetes and non-diabetics. And they're generally insensitive to the level of hypertension studied in the trial. So we see the same benefit when we start at a blood pressure of 130 and reduced to 120 as we do with the reduction in blood pressure from 150 to 140. So simply put a linear pattern of decrease in risk at least down to a blood pressure of probably 115 over 75. And as I mentioned, facts are pretty consistent across drug classes with a minor exception when we talk to -- about beta blockers which I will get to in a moment.

So what are the implications of this poor clinical practice? If we move to the next slide. Well, the first is that we talked a little bit about how we approach the problem about hypertension in general so that you know what the therapeutic armamentarium looks like in broad scale before we talk about the role of ALN-AGT.

The first is for everybody with blood pressure of more than 120, as you think about lifestyle modification, and really no conversation about hypertension therapy in the office should proceed without some discussion of what lifestyle factors the patient can engage in order to reduce blood pressure. And that's because the effects of lifestyle modification on blood pressure is quite potent and in some cases, maybe sufficient to [support] the need for pharmacologic therapy. Weight reduction is a piece of that, certain dietary approaches, including diets that are lower in sodium and higher in potassium such as the DASH diet. Restriction of dietary sodium intake to some extent, has an impact on blood pressure. Physical activity and moderation of alcohol intake are also key features of this and you can see the attributable reduction in blood pressure for each of these interventions.

I think that unfortunately, most patients and clinicians have not been all that successful in reducing blood pressure with lifestyle modification alone, so particularly for those with more significant hypertension pharmacologic therapy is typically needed.

If we move to the next slide, you'll see that pharmacological therapy in hypertension really is -- it's become a bit simplified. We think about -- because the reduction in risk is relatively insensitive to the type of therapy utilized, we just want to get the blood pressure down but there is a hierarchy of therapies that we consider based on the data from primary prevention trials. And there are specific populations where specific types of antihypertensive therapy are preferred. So for example, in diabetes, they prefer ACE inhibitors and angiotensin receptor blockers. In patients post myocardial infarction, we prefer beta blockers.

But in general, we approach the hypertension in the unselected population and to think about the ABCD [heuristic], where we begin with ACE inhibitors and angiotensin receptor blockers, and then consider beta blockers, calcium channel blockers and diuretics...

John M. Maraganore, Alnylam Pharmaceuticals, Inc. - CEO & Executive Director

Dr. Desai?

Akshay Desai,

Combination therapy -- yes?

John M. Maraganore, Alnylam Pharmaceuticals, Inc. - CEO & Executive Director

Dr. Desai, apparently the webcast has got a big echo in it, and we're trying to fix it right now. I just want to let the audience know that we are trying to fix the webcast audio. So Josh, do you recommend that Dr. Desai continues? Or what would you recommend at this point?

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

Yes. I think that's fine. Dr. Desai, you may continue but just to let the listeners at home know, we apologize. We are aware of the technical issue and that we're getting an echo on the webcast. The webcast is working to -- what's that?

Operator

This is the conference operator. Pardon the interruption. Dr. Desai, could you please turn off your computer speakers if you have them on.

Akshay Desai,

My computer speakers? Sure.

Operator

Please ensure that they are muted.

Akshay Desai,

Okay.

John M. Maraganore, Alnylam Pharmaceuticals, Inc. - CEO & Executive Director

Okay. So let's -- sorry about that, Akshay. Why don't you now continue? I think maybe that fixes it.

Akshay Desai,

Great. So I think what we -- so the intent of ABCD here is not sequenced the therapy in terms of priority but really just say that these are the drugs that we typically consider. Often patients with more significant hypertension get combination therapy upfront, for example, with an ACE inhibitor and a diuretic or an ARB and a diuretic or a calcium channel blocker and an ACE inhibitor.

I think what is relevant for this discussion is really that beta blockers have become a little less favored for treatment -- early-line treatment of hypertension, except in patients with particular indications for beta blockers. So those with low ejection fraction heart failure and hypertension might get a beta blocker because beta blockers are preferred in that population. Those with a prior myocardial infarction might get benefit from beta blockade, and therefore, those drugs are used.

But on the whole, in unselected patients with hypertension and no other risks, they are less effective than the other classes listed on the slide. And they're in -- compared to head trials with calcium channel blockers, there's a suggestion of higher rates of stroke in some studies with beta blockers due to, we think, to higher degrees of visit-to-visit variability, which may be related to adherence to the drug. There are certainly higher rates of discontinuation in that class. And so I think in general, although we think about all these drugs as commonly used for hypertension, the emphasis is on the A, the C and the D.

So if you move forward in the slide set, I think that all this that I've been providing to you really is to provide the groundwork for the SPRINT trial, which really tested in a systematic way this hypothesis that more aggressive blood pressure lowering to targets, that were previously thought to be well within the normal range, that is less than 120 millimeters of mercury, versus standard blood pressure reduction to less than 140 millimeters of mercury, that was the goal of the SPRINT trial was to see whether that more intensive strategy was more effective in preventing cardiovascular events than standard blood pressure intervention. So this is a large trial of nearly 9,300 patients who were older than the age of 50 and hypertensive and were known to be at slightly higher cardiac risk because they did have other risk factors. Patients were randomized to the strategy of intensive versus standard blood pressure control, as shown on the slide.

And what's critical about this trial is that the study was terminated actually earlier than anticipated by the Data Safety and Monitoring Committee because of overwhelming benefit at 3.3-year follow-up in the intensive arm. The blood pressure achieved in the intensive arm was about 122 millimeters of mercury versus 135 millimeters of mercury, again, that 10-point differential in blood pressure interventions, more hypertensives, antihypertensives used in the intensive group, about one more on average per patient.

But if you look at the slide, you can see that there are marked reductions in the intensive group in every category of efficacy, better -- fewer episodes of the primary outcome, which was a composite of myocardial infarction, acute coronary syndromes, stroke, heart failure or cardiovascular death. And even lower rates of all-cause mortality, which was reduced by about 27% with the more intensive blood pressure-lowering strategy.

There were side effects, more intensive approach, including hypotension and worsening renal function, which were more common in patients treated with the intensive strategy. And so there is a balance of risk and benefit to consider, but on the whole, overwhelming evidence supporting a more intensive blood pressure-lowering approach.

And it's really the result of the SPRINT trial, if you go to the next slide, that have driven changes in our practice guidelines. Now one of the questions that arises from SPRINT on the next slide is really how relevant the SPRINT population as to the total burden of hypertension. And I think this is worth going through just to give you a context of the burden of the problem. There are about 220 million U.S. adults with hypertension. About 95 of those -- 95 million of those are more than the age of 50. And the proportion who had a blood pressure more than 130 is probably another 37 million, of whom about 26 million have high cardiovascular risk.

And so it's really about a total of 17% of the treated hypertension population that is -- that would have been eligible for SPRINT. So this is a small proportion of the population but a not insignificant portion of the population that was studied in the trial, but at least makes the point that intensive blood pressure control has value probably down to a target of less than 120 millimeters of mercury.

And it's really this evidence, if you go to the next slide, that's evolved our thinking about how blood pressure should be treated and when it should be treated. The JNC 7 is the Joint National Commission, the seventh version or the last iteration. There is an eighth version, but let's look at the seventh, that gave us the cut points of 140 over 90 to define hypertension requiring treatment. And patients with blood pressure between 120 and 140 were called pre-hypertensive, and those were patients in whom generally lifestyle modification was encouraged, but there was no obligation to treat. Based on the data from SPRINT and the other data suggesting continuous effects of blood pressure reduction down to a blood pressure of about 115 over 75, the most recent iteration of the cardiovascular guidelines now defines blood pressures more than 120 as elevated, and hypertension requiring therapy begins at a blood pressure of 130 over 80. And so the goal for most patients, irrespective of comorbidity now, but perhaps the effect is amplified in those with comorbidity like diabetes or chronic kidney disease, is 130 over 80.

So what does this mean for the prevalence of hypertension? If you go to the next slide, you can see that by the new definitions, particularly in the younger end of the age scale, those defined as hypertensive are much greater in -- by the newer guidelines. We've now reclassified the number of people we thought were normal, particularly at the lower end of the age spectrum, as now hypertensive. And this means that there is a need for therapy in more patients under the new guidelines than would have previously been considered.

The next slide, and to give you some sense of what the population implications are. We've now reclassified about another 14% of patients post-SPRINT and post the guidelines as hypertensive. Another 2% to 3% likely require a pharmacologic therapy, and that equates to another 85 to -- 82 million to 83 million Americans.

And if you look at the last column in each of these graphs, you can see the large proportion of patients who are still not treated to goal. About 14% of the population by the new guidelines are undertreated, even though they are pharmacologically treated for hypertension.

So in the next phase of this brief talk, what I want to give you is some context for areas where we need more attention in hypertension therapy. The first is this problem of blood pressure variability. In general, we have utilized office blood pressures to define the initiation of medical therapy. And generally, we've never taken a single office measurement to define a threshold for intervention but rather average readings over several visits. And the mean of several visits is kind of -- in the office is usually used to trigger therapy.

The trouble is that blood pressure fluctuates both over the short term, depending on time of day. There's a known circadian variation to blood pressure. And over the long term, we know that there's a lot of inter-visit blood pressure variability. And because of that variability that's known well to clinicians, a lot of these episodic high values that we encounter in practice are disregarded by clinicians. And this may be one of the reasons for some therapeutic inertia, and no single value when encountered drives and change in therapy. But that may mean that patients who come to clinic are frequently unattended despite being persistently hypertensive and at risk for extended time intervals.

The emerging evidence that we have, and I'll show you some of this, suggests that this variability is not trivial and it's not simply statistical noise or inaccuracy in the blood pressure cuff, but it's actually meaningful from a risk standpoint and probably identifies patients to require more intensive intervention, particularly visit-to-visit variability rather than inter-visit variability really do carry prognostic importance.

I want to talk a bit about the day -- within-day variability of blood pressure. When we think about circadian variation, we're thinking about the way in which blood pressure varies over the 24-hour period, and here's an example of a 24-hour blood pressure recording in a patient. You can see that blood pressure takes the top curve here. Systolic blood pressure is relatively steady, but it's highest in the morning around the hours of 6 to 8 in the morning and then gradually fluctuates a little bit of volatility during the day, but then dips at night in the normal patient.

There is a phenotype of hypertension, which has been described, which is this concept of the non-dipper. These are people whose blood pressures don't dip during the night or even increase rather than dipping during the night, and those patients need -- tend to be those who are older, those with obesity and those with diabetes. And this phenotype of failing to dip or even reverse dipping, which means they're going up at night, is associated with higher risk. So the patients who have an inverted circadian pattern tend to be at particularly high risk, which sort of builds the case for tonic control of blood pressure and consistent control over the day.

And I think more than even the pattern over a 24-hour recording, we have data about just the blood pressure elevation at night. So if you look at the impact of nocturnal hypertension, so blood pressure elevation during sleep, in patients compared to the impact of hypertension during the daytime, recall that most of the data I've shown you is based on daytime blood pressures, you can see that there's a steady graded risk and a higher risk at every blood pressure point associated with nocturnal hypertension over daytime hypertension because at every threshold nocturnal blood pressure really ought to be lower.

If you go to the next slide, which really highlights the association between nocturnal hypertension and cardiovascular risk a little in association with other risk factors. So these are now modeling approaches looking at the risk of all cardiovascular events, coronary heart disease and stroke according in the first portion of the table, to the individual

variables, nocturnal blood pressure, daytime blood pressure and clinic blood pressure. And you can see that all parameters are associated with risk of each end point.

But when you simultaneously adjust for all of these parameters, you can see a much stronger association, in fact, the only association that persists with nocturnal blood pressure and with daytime or clinic blood pressure. And there's actually a lot more dispersion or variability in nocturnal blood pressure than daytime or clinic blood pressure. So what does this mean? Well it means that, in particular, we need to pay more attention and need to consider what's happening to blood pressure at night. And it's important for practice because we rarely get ambulatory blood pressure monitoring in our patients. And often, we're guided and reassured by good blood pressures in the office, which may mask a more significant hypertension during periods of the day.

The next slide really talks about diurnal variation of blood pressure but really what happens between visits. And as I mentioned, depending on when you take blood pressures, we know there's a lot of variability in the numbers we get. And this is data from 2 large trials, the U.K. TIA trial and the ASCOT blood pressure-lowering trial. And you can see that, that visit-to-visit blood pressure in the X-axis here is the standard deviation of between-visit blood pressure. And the more variability there is, there's a steady increase in the risk of stroke, perhaps a less [deep] increase in these studies in cardiovascular events. And these are studies in which the [effect of] variability was adjusted for the effect of mean blood pressure. So beyond blood pressure itself, which we know to be a risk factor, variability adds risk.

And if you look at the next slide from the VALUE trial, you can see that in higher-risk populations, and half of the people in VALUE had a prior myocardial infarction, this graded association with risk persists and maybe even more potent in -- with regard to cardiovascular risk. What's interesting is that the impact of variability, as shown in the highlight on the slide, may be greatest in those who are younger with hypertension, perhaps because there's less competing risk of other causes of myocardial infarction, stroke and death. But it really highlights the importance of variability, particularly in our younger patients.

I'll shift topics for a minute on the next slide and talk about another category where we need additional therapy, and this is this concept of resistant hypertension, which from the literature is defined as blood pressure that remains uncontrolled according to targets despite more than 3 antihypertensive medications. And the prevalence varies widely depending on the cohort examined in the last column of the slide, which shows you the variability of apparent treatment-resistant hypertension. That's that last column. You can see that the prevalence, depending on the population study, is somewhere between to 15% and 20% to 30%, depending on the cohort under study. But there are a lot of patients who remain uncontrolled despite more than 3 medications. And this is another circumstance in which the need for additional therapy becomes apparent because we know that treatment adherence is a function of the number of medications that patients take. And that it becomes harder for patients to adhere to therapy the more medicines we prescribe.

So moving to the next slide. Factors associated with inadequate blood pressure control to consider or lack of health insurance or access to care; absence of a usual source of care, that is a routine physician; failure to make the diagnosis of hypertension or to acknowledge that a given blood pressure is outside the target range; there's therapeutic inertia that we've talked about; a lack of education; and some underutilization of lifestyle modification; and there is also poor adherence to treatment. And I think we should add to this a lack of tonic control, which was raised in the opening remarks, but this concept of providing some background and consistent reduction in the baseline of blood pressure against which additional medications can act is an additional factor of risk, particularly given the variability that we've talked about.

I'll close with a note about adherence, and this is data showing longitudinal trends and different measures of adherence in a large sample of Medicare beneficiaries. And you can see in this slide, if we just look at the top line, which is the discontinuation rates that about 1/5 of patients -- or sorry, the bottom line, you can see that the discontinuation rates are about 1 and 5 for any hypertensive therapies. And those are pretty steady over time. But if you add to that the patients who don't take all of the medicines we prescribe or take them inconsistently, the number goes up to about an additional 30%. So as many as 40% of our patients or close to half of our patients are either poorly adherent or not taking the medicines we prescribe.

And on the next slide, you can see that adherence is another important predictor of risk. And those patients, particularly who are low or intermediate in their adherence to find that the proportion of the prescribed days of coverage they actually take really don't seem to get nearly as much benefit as those who are extremely adherent. And this should be obvious that if patients don't take medicines, they don't get the benefit. But I think it's another target for improvement in our therapy. The high-adherent patients, the ones who took at least 80% of their medicine, had a 38% lower risk of cardiovascular medicine than those who had lower rates of adherence.

So when we think about adherence, one of the challenges in adherence is, as I mentioned, the pill burden. The multi-pill regimens are associated with far higher rates of discontinuation. If patients have to take medicines multiple times a day, they don't adhere quite as much as we would like. And then there are a number of other factors, which may be less modifiable, including behavioral factors, depression, access to care. But adverse medication effects are certainly on that list.

If you move to the next slide, I'm going to close with a note about therapeutic inertia, and this really is our problem as clinicians, which is that if you look at the large pool of ambulatory visits where hypertension has been identified, only a small fraction in the red circle are actually intervened. And this is, as I mentioned, in part related to the fact that people want to limit their action based on a single blood pressure or concerned about side effects or maybe there's just not time in the visit to address blood pressure or other things take precedence. But these rates are relatively consistent over time and reflect a really unmet need and missed opportunity for aggressive blood pressure reduction in our population. And so this is another area that needs to be addressed.

So the last slide is my conclusion, which is to remind you about the -- there is a continuous and graded association between systolic or diastolic blood pressure and the risk of cardiovascular events that persists down to a blood pressure of about 115 over 75. The more aggressively we control blood pressure, the more we see reduction in cardiovascular events and mortality. A large proportion of patients with hypertension are untreated, and resistant hypertension is more common than we might have expected. Short- and long-term variation in blood pressure are tightly coupled to risk even after adjustment for mean pressure and can be modulated with pharmacologic therapy, either for bad, as with beta blockers; or for good, as has been seen with calcium channel blockers. And non-adherence and therapeutic inertia probably contribute to some of the inadequate blood pressure control we see in practice.

So I hope that provides you with some context, and I'll hand it back to the moderators to continue the discussion.

Jae B. Kim,

Thank you, Dr. Desai. Can you advance to the next slide, please? It's my pleasure to go over some of the ALN-AGT background and the development program. Dr. Desai has outlined the immense public health problem of hypertension globally. In the past year, the American Heart Association took the extraordinary step of declaring an urgent call to action. Previous reductions in cardiovascular mortality has, in fact, declined and diminished and even reversed in some populations. Cardiovascular disease remains the leading cause of death in the United States and in the Western world. And high blood pressure is the #1 preventable cardiovascular risk factor for premature mortality in the United States.

In the left-hand panel, you see that high blood pressure accounts for approximately 400,000 deaths per year in the United States alone. Hypertension leads to strokes and heart attacks and is the leading cause of death and disability in adjusted life years worldwide. 45.6% of U.S. adults have hypertension under the new 2017 ACC/AHA guidelines for hypertension, and more than half of patients on medications remain above their blood pressure targets. And despite the availability of antihypertensives, there is, as Professor Desai had articulated, poor adherence, blood pressure variability that's largely unaddressed, inadequate nighttime control of blood pressure and increasing prevalence of resistant and refractory hypertension. This highlights the desperate need for manifold innovation for new therapeutics that not only have enhanced efficacy and safety, but also therapeutics that address patient behavior and problems of poor compliance.

Next slide, please. We bring your attention to lessons learned from inclisiran, an investigational RNAi therapeutic targeting PCSK9 that Alnylam has partnered with Novartis on its -- on the development of inclisiran with The Medicines Company. And inclisiran has shown highly stable and durable efficacy and similar safety to comparable to placebo. And in this figure, we show percent change in LDL-cholesterol over time and the pooled ORION Phase III analysis of approximately 3,660 patients. Here, looking at the LDL-cholesterol over time, you see the clamped pharmacology and class pharmacodynamics of inclisiran that's achieved with tonic reduction in LDL-cholesterol. Additionally, safety observations in approximately 7,000 inclisiran injections and greater than 2,700 years of patient exposure show inclisiran safety profile that is similar to placebo and no adverse changes in laboratory markers. We believe that this type of profile should be achievable with ALN-AGT.

Next slide, please. To summarize the therapeutic hypothesis for ALN-AGT, which provides the potential for a differentiated profile to improve cardiovascular health as opposed to conventional small molecule therapeutics. ALN-AGT has liver-specific silencing. And therein, we believe that there's a mechanistic potential advantage for improved renal safety. And we believe there might be an opportunity for enhanced efficacy through this unique mechanism of action that targets the source of vasoactive peptides. And due to the stable and durable silencing of Alnylam siRNA therapeutics, we may be able to address nighttime blood pressure, blood pressure variability and adherence problems.

In totality, we think that we could potentially achieve enhanced efficacy with a wider safety margin. These could translate into potential clinical advantages that include potent, durable and stable reductions in blood pressure, use with or without an ACE inhibitor ARB. And these should translate into reductions in stroke, myocardial infarction, heart failure and kidney disease.

Next slide, please. Nonclinical data in animal models with ALN-AGT are promising. Here, we show angiotensinogen silencing results in blood pressure lowering in a rat spontaneous hypertension model. In the left-hand panel, we show

that ALN-AGT siRNA reduced blood pressure, and the combination of AGT siRNA plus valsartan, an ARB resulted in synergistic blood pressure reduction greater than captopril and valsartan.

And not shown here, though, is that AGT siRNA in this rat SHR model showed that the AGT plus valsartan was the only therapeutic combination -- oral combination that normalized cardiac hypertrophy in this model.

And on the right-hand side, you see that despite the extreme blood pressure lowering that was achieved with ALN-AGT, with AGT silencing plus valsartan, there were a number of preclinical safety parameters in AGT siRNA with or without valsartan that were reassuring. One, there were no reflexive changes in heart rate. There were no reductions in activity that was tracked by radiotelemetry. There's no decrease in urine output. And there was no change in directly-measured glomerular filtration rate. It's a biomarker of renal function. And there were no acute kidney injury as measured by neutrophil gelatinase-associated lipocalin or NGAL. It's an early biomarker for kidney injury that precedes changes in kidney function. The initial promise in animal models paved the way for clinical study in humans.

Next slide, please. So ALN-AGT for hypertensive diseases follow the Alnylam clinical development model to maximize our chances or probabilities of success. Our target selection was a genetically validated liver-expressed target chain. Angiotensinogen, I don't know if you are aware, was the first gene linked to primary hypertension. Here we show in Cell, back in 1992 with the first publication of the linkage. And this was seminal work by Professor Rick Lifton, who's currently President of the Rockefeller University. And the development is also facilitated by a measurable biomarker for proof-of-concept in Phase I. And here we are fortunate that we could track pharmacodynamics by a CRM biomarker for angiotensinogen levels and a clinical biomarker in the form of blood pressure measurements. There is also a definable path to approval and patient access. Blood pressure is, in fact, considered by global health authorities a validated surrogate for fatal and nonfatal stroke and myocardial infarction.

Next slide, please. On this slide, we summarize the clinical development path for ALN-AGT. Now hypertension is such a huge public health problem that for drugs indicated to lower blood pressure over the treatment of hypertension to lower blood pressure, the FDA had released a guidance recommending to the labeled indication that you have language that states: "lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infractions." That is robust testimony from the U.S. FDA that hypertension is such a profound public health concern that they would take the extra step of translating the surrogate of blood pressure change to cardiovascular outcomes in the label indication.

Now here, we show our Phase I, II and III progressions. Phase I is an n of approximately 200 patients. Phase II, we incrementally grow the clinical experience with hundreds of patients, and Phase III will likely be thousands. And we plan to study ALN-AGT as monotherapy and in combination with standard of care. And as we progress to early, mid- and late development, we will enrich the population being studied, inclusive of patients with high CV risk and resistant hypertension.

There are well-established endpoints and precedent for the basis of approvals in hypertension. They include systolic and diastolic blood pressure by clinic blood pressure measurements, and 24-hour mean systolic and diastolic pressure by ABPM or ambulatory blood pressure monitoring.

Also with the unique mechanism of action and achieved pharmacokinetic -- pharmacodynamics of ALN-AGT, there's an opportunity for novel endpoints subject to alignment with regulators, which includes various approaches to measuring blood pressure variability, wherein siRNA therapeutics may provide a unique advantage and nighttime blood pressure and nighttime dip, and also that we will be able to study in the real world, perhaps improved adherence and compliance by virtue of such a durable therapeutic.

Next slide, please. On this slide, we show the ALN-AGT first-in-human single ascending dose study, wherein we're very happy to share that initial human proof of concept was achieved. The patient population were adults, hypertensive by clinic measurement and also ABPM. And secondary hypertension was excluded. Cohort sizes of 12 patients were randomized 2:1 into single ascending dose cohorts. And we had completed dosing in 6 cohorts and completed acquiring data up to 200 milligrams. And endpoints included safety and tolerability, AGT levels, PK and PD and systolic and diastolic blood pressure reduction. We have additional cohorts planned to evaluate the use of ALN-AGT in obese patients who will measure PK/PD and effect of ALN-AGT on blood pressure and body composition. We plan to have a salt control cohort, where we evaluate the tolerability with salt depletion. And this provides a challenge very much like dehydration of volume depletion that might occur in the world and also recovery of blood pressure or rescue with high salt. This should provide a strategy for chronic -- for outpatient management with ALN-AGT for patients who have low blood pressure that they could even take a high amount of salt to recover blood pressure in terms of management. And the addition of ARB in the background of ALN-AGT where we evaluate safety and tolerability with the combination with ARB.

Next slide, please. As we have previously announced, we are exuberant to announce that -- at the announcement that initial proof of concept was achieved with ALN-AGT, a number of observations from the initial Phase I single ascending dose top line results can potentially address numerous unmet needs. We have shown that we can achieve 90 -- greater than 90% knockdown of angiotensinogen that demonstrates that we have achieved a clamped

pharmacology with ALN-AGT. We've also achieved greater than 10-millimeter reduction in mean 24-hour systolic blood pressure relative to placebo. And this could potentially address uncontrolled blood pressure with stable blood pressure reduction and possibly less variability in blood pressure and possibly tonic control with blood pressure with nighttime blood pressure lowering.

We have also shown durability supportive of once quarterly and possibly less frequent dosing. And this may potentially resolve adherence problems common with current daily oral medications. We have also shown encouraging safety and tolerability with no drug-related SAEs. And we are hopeful that ALN-AGT in the clinical development program may demonstrate an improved safety profile that may be achievable with or without ACE inhibitor or ARB. And we -- to be informed by data in the program. These results are planned to be presented at a scientific meeting in late of this year.

And I'm happy to hand the presentation to Lauren Melton.

Lauren Melton,

Thank you, Dr. Kim. My name is Lauren Melton, and I will now review the global commercial opportunity for ALN-AGT. Next slide, please. When considering the future commercial populations for ALN-AGT, we consider 2 patient segments. The first patient segment includes patients with uncontrolled blood pressure at high risk for major adverse cardiovascular events. We have estimated the U.S. prevalence of this population be between 5 million and 16 million people. The population is defined as patients being treated for hypertension with uncontrolled blood pressure and with a previous medical history of myocardial infarction, angina, stroke, transient ischemic attack, heart failure, peripheral arterial disease or type 2 diabetes.

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 and specific comorbidities that the patients may have. For the treatment of their hypertension, patients are often prescribed into 1 or 2 antihypertensives, with additional agents being added or doses increased to achieve blood pressure in the target range. As many of these patients are taking medications to address multiple comorbidities, pill burden is significant and adherence is often suboptimal. Lack of adherence is of utmost concern in patients at high risk for cardiovascular events where uncontrolled blood pressure can lead to poor clinical outcomes.

The disease burden of hypertension is significant. Uncontrolled hypertension is the major risk factor for cardiovascular disease morbidity and mortality. And annually, approximately 1.5 million people in the U.S. suffer from myocardial infarction and stroke, with approximately half of these major adverse events attributed to hypertension. The burden of hypertension in health care cost is also quite significant. Annual direct and indirect cost of hypertensive diseases and stroke is estimated to be at $55 billion and $45 billion. And while only approximately half of the stroke costs are attributed to hypertension, additional health care costs are incurred due to hypertension within the broad category of heart disease.

Further, suboptimal blood pressure control cost $370 billion in 2001 and is estimated to be approximately 10% of the world's overall health care expenditure at that time. 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 cardiovascular events, we estimate ALN-AGT could achieve global revenues that are greater than $2 billion at peak.

Next slide, please. The second commercial patient population is the resistant hypertension patient segment. This patient population has significant unmet need for new therapies that can further lower blood pressure and reduce blood pressure variability. The prevalence of this population in the U.S. and EU is estimated at 20 million, with 11 million patients in the U.S. alone. Resistant hypertension is defined as uncontrolled blood pressure on 3 antihypertensive agents or use of 4 or more antihypertensive agents independent of whether blood pressure is controlled within target range. It is estimated that 20% of drug-treated hypertension is considered resistant, with approximately 10% of treated patients being prescribed 4 or more anti-hypertensive medications and often at maximally tolerated doses.

The resistant hypertension disease burden is quite high, and patients with resistant hypertension are at higher risk for poor clinical outcomes, including death, myocardial infarction, heart failure, stroke or chronic kidney disease, as compared to patients with nonresistant hypertension. Similar to patients with high cardiovascular risk, non-adherence is prevalent with approximately 30% of patients being sub-optimally treated due to non-adherence, often attributed to highly daily pill burden. The cost of resistant hypertension remains the same as that of high risk -- of the high-risk patient segment with uncontrolled hypertension. Annually within the health care system, greater than $50 billion in direct and indirect costs are related to hypertensive disease.

Given the unmet medical need for agents that can stably further reduce blood pressure in patients with resistant hypertension, we believe ALN-AGT could be a greater than $2 billion global market opportunity at peak.

The next slide, please. In summary, there is significant unmet medical need for treatment of hypertension in patients with uncontrolled blood pressure. Importantly, sustained blood pressure control with infrequent dosing could benefit

patients with difficult-to-treat hypertension or patients at risk for cardiovascular events with uncontrolled blood pressure. Initial data from the ongoing Phase I study in patients with mild to moderate hypertension are encouraging. The safety and tolerability profile continues to appear favorable. We've observed greater than 10-millimeter persistent reduction in mean 24-hour systolic blood pressure relative to placebo. The pharmacologic durability is supportive of once quarterly and potentially less frequent dosing. And additional clinical data are expected to be presented at a Scientific Congress later this year.

Lastly, the next development milestone includes initiation of Phase II studies in 2021. In those studies, we will explore use of ALN-AGT both alone and in combination with standard-of-care antihypertensive medications. Thank you for listening, and now I'll turn the discussion back over to John for the Q&A portion of this presentation.

John M. Maraganore, Alnylam Pharmaceuticals, Inc. - CEO & Executive Director

Thanks, Lauren. And why don't we dive into the Q&A. And I think we can go a little bit after 3:30, just because we have a number of questions here.

QUESTIONS AND ANSWERS

Answer – John M. Maraganore: Let me start with some questions for Dr. Desai. One of the questions related to the slide you showed on doubling of risk for every 20 over 10, the doubling of cardiovascular mortality risk, as I recall, for every increment of 20 over 10 in blood pressure. And the question really is, what portion of it comes from systolic versus diastolic? Or is it both?

Answer – Akshay Desai: Yes. So it's a great question. And I think our -- the observation is that, certainly, in the elderly, systolic hypertension is increasingly more common than -- but I think the relationship is with both. Smaller increments in diastolic blood pressure contribute to risk than increments in systolic blood pressure, but which is why we use that 20 over 10 threshold. But effectively, whether it's a 10-millimeter increment in diastolic blood pressure or a 20-millimeter increment in systolic blood pressure, we see that same doubling of risk. So I think it's both. But in the elderly and in common practice, I think systolic blood pressure is often the more relevant target.

Answer – John M. Maraganore: Okay. Thank you. And another question for you, Dr. Desai, is why do existing antihypertensive medicines not provide sufficient control for nocturnal blood pressure? Is there a known mechanism for that?

Answer – Akshay Desai: Well, I think that the precise mechanism, I'm not sure is well understood. I think that the -- part of the issue is probably durability and consistency of action. So most of our medicines, even the ones that are dosed once a day, do have some waning of effect after they reach their peak. And so it's conceivable that the effect of medicines taken during the early portion of the day is lost by nighttime, which is one of the reasons that in clinical practice, we often ask patients to take at least some of their antihypertensives prior to bedtime so that we divide the dosing of medicines or spread the effect over the day.

The other may be that there are other features which contribute to the risk of nocturnal hypertension in particular that are unattended with some of our existing antihypertensive. That's something we need -- the mechanisms by which nocturnal hypertension happens is a little unclear. But some of the things that might be also relevant are comorbidities that drive blood pressure elevation at night. So anything that activates sympathetic nervous system activity during the nighttime may drive blood pressure elevation. So untreated sleep apnea, for example, may contribute. You saw that obesity and age are other factors.

So I think it's partly the lack of duration of [effect of] medicines, the distribution of medicines over the day, the fact that medicines tend to be concentrated in administration earlier in the day and not divided, and then I think also peculiar risk factors for nocturnal hypertension that are not addressed by standard therapy.

Answer – John M. Maraganore: Thank you. And then maybe following up on that, and this is a question that, Jae, you may also want to add some perspective after Dr. Desai, is how would you measure effects on variability and on nocturnal blood pressure in a registrational trial? What are the sort of -- are the approaches in hand to be able to do that?

Answer – Akshay Desai: I think the most [ready] approach if we're looking at diurnal variation in blood pressure is 24-hour ambulatory blood pressure monitoring, which has been embedded within a number of trials, including some of the ones I showed. I think the visit-to-visit variability or longer-term variation in blood pressure, I think, is largely drawn from serial office visit data from patients in clinical practice. And I think with frequent follow-up visits during the course of a trial would also -- is also something that could be measured over time. So I think that -- at least those are some thoughts. Jae, I don't know if you have other general ideas there.

Answer – Jae B. Kim: Yes. No, that's terrific, Dr. Desai. Yes. It's -- the approaches to measuring nighttime blood pressure -- and as you said, nighttime dip and also visit-to-visit variability, have some fair amount of prior precedent. And we look forward to evaluating these measures as observational data have shown that these are all independent

risk factors in addition to or even when adjusted for mean blood pressure. So we think that there's a great deal of promise for an investigational therapeutic that has tonic control of angiotensinogen to affect those parameters.

Answer – John M. Maraganore: Okay. Thank you, Jae. And then another question on the clinical development path a little bit. And maybe, Jae, this would be for you. And Lauren, you may comment as well. It's would the registrational path require an outcome study for approval and/or for payer discussions? So maybe, Jae, you could comment on the approval. And Lauren, you can comment on the payer side of it.

Answer – Jae B. Kim: Yes. And that's a terrific question because the U.S. FDA had already opined about that. They published an FDA guidance to industry to state that blood pressure is a validated surrogate for outcomes and therapeutic agents that are designed, and with blood pressure as the endpoint will also have the recommended indication language that blood pressure is a source of risk for cardiovascular events, primarily stroke and myocardial infraction. So for regulatory purposes for registration and approval, antihypertensive agents primarily need to show an effect on blood pressure and do not need to show outcomes.

Answer – John M. Maraganore: And Lauren, do you want to comment on the payer side of it?

Answer – Lauren Melton: Sure. I think it's important to note that ALN-AGT is an innovative medicine that we expect will deliver value to patients and prescribers, particularly patients that are at high risk for adverse cardiovascular events or patients with very difficult-to-treat hypertensions such as resistant hypertension.

We do acknowledge, as Jae noted, that blood pressure is an approvable clinically validated surrogate endpoint for the purposes of regulatory approval. And we'll have discussions with payers and -- regional payers because there may be differences around the globe as to what the expectations would be for outcomes data. And we'll do that in parallel with development programs.

Answer – John M. Maraganore: Okay. Thank you. And so just one question that comes up on the safety side is what's the -- what's -- is there a theoretical risk of hypotension with this mechanism? And maybe, Dr. Desai, you can comment. And then, Jae, you can comment as well. I think maybe both of you could have a perspective on that.

Answer – Akshay Desai: Sure. I'm happy to start. So I think that with any medicine with long duration of action, I think there is always some concern about what to do when blood pressure gets low for other reasons. So the circumstances we would worry about that are in patients who've become -- I think in chronic practice, the effect here is we anticipate will be relatively predictable. With most antihypertensive drugs, that's the case. But anybody on antihypertensive therapy who develops hypotension for another reason is at risk if they continue to take their antihypertensive drugs. And the longer the duration of action of the drugs, the harder it might be to reverse that effect. And so I think there is some concern that needs to be attended in the trials around what that risk is.

I think the obverse of that is that in most cases of antihypertensive drug-associated hypotension, we're often able to rescue therapy with volume resuscitation, salt loading, sometimes administration of vasoconstrictors. And so I think another aspect would be to see whether that's the same case here.

Jae, you could speak much more to the specifics of the ALN-AGT approach.

Answer – Jae B. Kim: Yes. I think there are some to be borne out by further clinical data is that there are some, I believe, inherent advantages for an siRNA therapeutic in terms of hypotension. And that is a gradual and durable pharmacology. There is some component of hypotension or clinically meaningful hypotension that may result from the compliance or the fluctuations related with small molecule therapeutics.

In clinical models, significant knockdown in normal -- in actually healthy primates, despite massive reductions in blood pressure, the primates had no clinical symptomatology of hypotension and have normal activities. And our clinical trials will evaluate the effects on lowered blood pressure with ALN-AGT. And to date, no patient in the Phase I study had developed a hypotensive event despite greater than 90% knockdown and despite the efficacy, as we had shared with you in the proof of concept.

We will gain further insight into this risk as we continue to dose-escalate. And we will also evaluate for -- what will happen with augmented pharmacology by introducing salt depletion and in a directly monitored setting to evaluate just what -- exactly what Dr. Desai had highlighted is that some people may have an accident or they may bleed or something. And here, we will show really reciprocate in humans what we had already shown in a nonclinical study that high salt can rescue blood pressure, which has profound impact on how this could be clinically managed, which is to say that traditional volume resuscitation measures can be used to rescue patients with ALN-AGT.

We have also conducted preclinical experiments that show standard treatments for low blood pressure. That includes standard high salt and vasopressor agents that they're effective for hypotension in nonclinical study. So at a high level, I think that there is a lot of promise and potential that for ALN-AGT standard clinical measures to manage low blood pressure can be adopted for the management of -- if hypotension should occur, ALN-AGT can be used.

Answer – John M. Maraganore: Okay. That's helpful, Jae. And maybe this could be our last question. And I think maybe, Jae, you might be the best one to answer this. But as you think about safety, how does this program compare to the early inclisiran clinical experience? And Jae, of course, you were deeply involved with that clinical experience. I don't know if you have any perspectives on that.

Answer – Jae B. Kim: Yes. It's -- I would say that ALN-AGT has borne out initial clinical data that is very similar to inclisiran. That is to say that we are achieving a high degree of efficacy, durable clamped pharmacology with a durable knockdown that is -- and with the safety profile that is initially highly encouraging and no evidence of any biomarker abnormalities that would be concerning clinically. So I'd say the promise for ALN-AGT and bearing out a profile like inclisiran is forefront in our attention.

Answer – John M. Maraganore: Great. Well, that's great. I think that's a good place to end. Dr. Desai, we want to thank you for participating today. Sorry to everybody on the audience for the echo we had at the beginning of the call. And thanks for everybody for joining today, and enjoy the rest of your day and stay safe. Thank you very much.

Answer – Joshua Brodsky: Thanks, John. Thanks to all our speakers, and thanks to you for listening. This concludes today's roundtable. 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 the next RNAi Roundtable on Friday, July 17. Please be sure to visit Capella for all of the latest on the dates and times of the additional roundtables in the series. Thanks, everyone. Have a great day.

Answer – John M. Maraganore: Bye-bye.
