FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE (CRDAC) MEETING

Virtual Meeting

Wednesday, September 13, 2023

9:00 a.m. to 4:19 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Joyce Frimpong, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. BUTLER: Welcome. I would first like to remind everyone to please mute your lines when you're not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her e-mail is currently displayed.

My name is Dr. Javed Butler, and I will be chairing this meeting. I will now call the September 13, 2023 Cardiovascular and Renal Drugs Advisory Committee meeting to order. Dr. Joyce Frimpong is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. FRIMPONG: Good morning. My name is Joyce Frimpong, and I'm the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Bairey Merz?

DR. BAIREY MERZ: Good morning. Noel Bairey

Merz, cardiology, Cedars-Sinai Heart Institute, women's health and investigative ischemic heart disease. Thank you.

DR. FRIMPONG: Dr. Butler?

DR. BUTLER: Javed Butler, heart failure cardiologist, Baylor Scott and White Health, Dallas, Texas.

DR. BUTLER: Thank you.

Dr. Kasper?

DR. KASPER: Ed Kasper, heart failure cardiologist, Johns Hopkins.

DR. FRIMPONG: Dr. Kovesdy?

DR. KOVESDY: Good morning. Csaba Kovesdy, nephrologist, Memphis VA Medical Center and University of Tennessee Health Science Center, Memphis, Tennessee.

DR. FRIMPONG: Dr. Moliterno?

DR. MOLITERNO: Hi. David Moliterno. I'm a cardiologist at the University of Kentucky.

DR. FRIMPONG: Dr. O'Connor?

DR. O'CONNOR: Good morning. Christopher O'Connor here. I'm president of the Inova Heart

and Vascular Institute in Northern Virginia and a heart failure cardiologist.

DR. FRIMPONG: Dr. Peterson?

DR. PETERSON: Good morning. Eric Peterson, cardiologist, vice provost for clinical research at UT Southwestern, Dallas, Texas.

DR. FRIMPONG: Dr. Roy-Chaudhury?

DR. ROY-CHAUDHURY: Good morning. Prabir Roy-Chaudhury. I'm a transplant nephrologist at the University of North Carolina at Chapel Hill and at the Salisbury VA Medical Center.

DR. FRIMPONG: Dr. Thadhani?

DR. THADHANI: Good morning. Ravi Thadhani, executive vice president for Health Affairs at Emory University. Thank you.

DR. FRIMPONG: And for our industry representative, Dr. Soergel?

DR. SOERGEL: Good morning. David Soergel, global head, Cardiovascular, Renal, and Metabolism Development at Novartis.

DR. FRIMPONG: Ms. Abernathy?

MS. ABERNATHY: Rita Abernathy, retired

architect and ATTR-V patient, Washington, DC area.

DR. FRIMPONG: Dr. Cella?

DR. CELLA: David Cella. I'm a psychologist, professor at Northwestern University, and a clinical outcomes assessment researcher.

DR. FRIMPONG: Dr. Smith?

DR. WILDER SMITH: Good morning. Ashley Wilder Smith. I am chief of the Outcomes Research Branch at the National Cancer Institute, part of the National Institutes of Health.

DR. FRIMPONG: Alright. And now for our FDA participants, when I call your name, if you could please come to the podium and introduce yourself.

We have Doctor Joffe.

DR. JOFFE: Good morning. I'm Hylton Joffe, the director of the Office of Cardiology, Hematology, Endocrinology and Nephrology in CDER at FDA.

DR. FRIMPONG: Dr. Stockbridge?

DR. STOCKBRIDGE: Good morning. I'm Norman Stockbridge. I'm the director of the Division of Cardiology and Nephrology.

DR. FRIMPONG: And Dr. Adigun.

DR. ADIGUN: Good morning. I'm Rosalyn Adigun, clinical reviewer, Division of Cardiology and Nephrology. Thank you.

DR. FRIMPONG: Thank you.

Dr. Butler, I will now hand it back over to you.

DR. BUTLER: Thank you, Dr. Frimpong.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting be a fair and open forum for the discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

Also, in the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at

hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Dr. Frimpong will read the Conflict of Interest Statement for the meeting now.

Conflict of Interest Statement

DR. FRIMPONG: Thank you, Dr. Butler.

The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that that agency's need for a special government employee's services outweigh their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of

this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of supplemental new drug application 210922-s015 for Onpattro, patisiran, lipid complex for injection, submitted by Alnylam Pharmaceuticals, Incorporated, for the treatment for the proposed treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults.

This is a particular matters meeting during which specific matters related to Alnylam Pharmaceuticals, Incorporated sNDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no

conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we're encouraging all standing members and temporary voting members to disclose any public statements they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. David Soergel is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Soergel's role at this meeting is to represent industry in general and not any particular company. Dr. Soergel is employed by Novartis.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants

to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. BUTLER: Thank you, Dr. Frimpong.

We will now proceed with the FDA introductory remarks from Dr. Norman Stockbridge.

FDA Opening Remarks - Norman Stockbridge

DR. STOCKBRIDGE: Good morning again. Norman Stockbridge. I want to first thank the committee for the time they've already spent and the time that they will be spending today in support of this public health service.

I want to make a couple of comments about responder analyses, which are likely to be a topic that comes up through the day. First of all, whenever you have a bell-shaped distribution and provide some portion of it with a small incremental benefit, even if that benefit is, let's say, 2 percent and applies to everybody, if you then look at the characteristics of people who have a later response that's above some threshold you've set for responders, there will obviously be more in

the group that had the boost than in the unboosted group, and that proportion of people who were in the responder group will get larger, the larger you set the boundary for the response threshold.

This is a property of the shape of the original distribution and has nothing, really, to do with anything about identifying a responder group. It's also true when the measurement that's under consideration is stable -- that is, patients respond the same every time you ask them a question or when there's real variability -- real variability shows up in individual patient responses because of variability in the manifestations of the disease from one day to the next, factors that are unrelated to the disease itself but affect the measurement that you're trying to make, and also measurement errors.

This variability within subjects is responsible for the phenomenon that you may know as regression to the mean. When you take a population, select from it people who have a measurement that's above or below some threshold,

randomize them and make the measurement again, you will often see that people show up with measurements that would have gotten them excluded from the study originally, and that phenomenon is known as regression to mean.

This phenomenon of regression also happens with respect to responder thresholds. If you set a threshold and see a group of people who meet that threshold on one visit, they are not likely to be the same people who would show up there on a subsequent measurement. This, I assert, means that a single observation of people above a certain response threshold is a poor indicator of a responder population. Thank you.

DR. BUTLER: Thank you, Dr. Stockbridge.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based on the outcome of the meeting.

Likewise, the FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Alnylam Pharmaceuticals' presentation.

Applicant Presentation - Pushkal Garg

DR. GARG: Good morning, everyone. My name is Pushkal Garg, and I'm the chief medical officer at Alnylam, a company focused on discovering and developing RNAi therapeutics. On behalf of

Alnylam, I want to thank the members of the advisory committee and the FDA for the opportunity to present to you today on our supplemental NDA for patisiran, for the treatment of cardiomyopathy of ATTR amyloidosis.

ATTR amyloidosis is a rare, multisystem, rapidly progressive, and ultimately fatal disease that's caused by the misfolding of transthyretin or TTR. TTR is a hepatically produced protein that primarily serves to transport vitamin A. But in the setting of mutations, variant TTR, which leads to the hereditary form of the disease, or with aging, wild-type TTR, can misfold and form amyloid fibrils. These amyloid fibrils deposit in the peripheral nerves and the heart to cause the polyneuropathy and the cardiomyopathy that are the hallmarks of this disease.

Patisiran is a small interfering RNA that targets a highly conserved region of the TTR gene found in both variant and wild-type forms. It's formulated as a lipid nanoparticle for liver-specific delivery and is administered

intravenously at a dose of 0.3 milligrams per kilogram every 3 weeks. When administered, patisiran is taken up by the liver, where it inhibits hepatic synthesis of both variant and wild-type TTR by the process of RNA interference at their source and before they can form amyloid-causing monomers. This results in lower circulating levels of the pathogenic protein TTR, reducing further amyloid deposition in the nerves and the heart, and thereby stabilizing or even improving the manifestations of this disease.

The first test of patisiran's efficacy was in the phase 3 APOLLO study in patients with polyneuropathy due to the hereditary form of ATTR amyloidosis, which led to the initial approval of patisiran in 2018. In that study, patisiran rapidly and sustainably reduced serum TTR by over 85 percent.

The impact of this TTR reduction on neuropathy impairment and quality of life is shown in the middle and right panels, respectively. The steady progressive nature of the disease is evident

from the trajectory of the placebo patients, who experienced steady worsening over just 18 months. In contrast, patients given patisiran experienced significant benefit with stabilization and even improvement compared to baseline in both neuropathy impairment and quality of life, with benefits seen as early as 9 months.

Importantly, more than half of the patients in the APOLLO study had evidence of concurrent cardiac amyloidosis according to predefined criteria, which enabled evaluations of the impact of patisiran and the cardiac manifestations of this disease. These assessments indicated that patisiran improved cardiac structure and function over 18 months, with an approximate halving of the risk of all-cause mortality and CV hospitalizations.

Thus, these results from the APOLLO study, in addition to other published case reports and case series, indicated that patisiran may also be of benefit to ATTR patients with cardiomyopathy, thereby forming the basis for the APOLLO-B study

we're here to discuss today.

Patisiran received orphan drug designation for the treatment of ATTR amyloidosis, encompassing both polyneuropathy and cardiomyopathy in December of 2017, and was approved for polyneuropathy in August of 2018. In December of that same year, we aligned with the agency on a single study in patients with cardiomyopathy with the 6-minute walk test 12 months as the primary endpoint and the Kansas City Cardiomyopathy Questionnaire as the first secondary.

Selection of these endpoints was consistent with FDA guidance issued in 2019, that stated that functional ability or symptoms could serve as approvable endpoints in heart failure. Another consideration of the design of the study was the approval of the TTR stabilizer, tafamidis, just around the time of study initiation. My colleague, John Vest, will explain how that was addressed in the study design.

APOLLO-B enrollment began in September of 2019 and completed in June 2021, with top-line

results in August of 2022. APOLLO-B was positive, showing benefits on both patient function and symptoms in patients with ATTR cardiomyopathy. We observed that patisiran lowered TTR, the pathogenic protein, by more than 85 percent. By doing so, it slowed the decline in functional capacity, as measured by the 6-minute walk test, to a rate comparable to normal aging.

It also stabilized patient health status, symptoms, and quality of life, as measured by the KCCQ, and it led to improvements of the clinically relevant cardiac biomarkers, NT-proBNP and troponin I. In fact, the APOLLO-B results closely mirrored the benefits of patisiran that were seen in the polyneuropathy aspects of the disease in the original APOLLO study, where we also saw functional, health status, and biomarker changes.

Thus, the efficacy of patisiran cardiomyopathy is supported by confirmatory evidence from APOLLO. Importantly, patisiran demonstrated a favorable safety profile in APOLLO-B, consistent with the profile observed in APOLLO,

and 5 years of postmarketing experience.

In our presentation today, we will explain why these observed benefits of patisiran are clinically meaningful and address important patient needs. You'll hear from our clinical experts that patients with this disease were typically in their 70s and 80s and greatly value their ability to maintain function and health status and minimize their heart failure symptoms. But unfortunately, despite an approved TTR stabilizer, disease progression is common.

This unmet need is highlighted by rapid enrollment in a patisiran expanded access program established after the APOLLO-B results were known. The program was set up at just 20 U.S. centers for patients who are experiencing progression on TTR stabilizer and enrolled very quickly at a rate of approximately 5 patients per week, filling up in just 10 months. And specifically to the questions posed by the FDA, the study results demonstrate that the benefits shown are very meaningful.

Patisiran reduces disease progression as

assessed by multiple complementary measures, including the objective evaluation of function, patient-reported health status and symptoms, and clinician assessments, in contrast to the inexorable progression that patients otherwise experience, and it's well tolerated with no major safety concerns. At the same time, it's important to acknowledge an important limitation of the data, which is that the effect of patisiran when given in combination with tafamidis has not been established. We believe this limitation can be readily communicated in the product label.

Thus, based on these data, we believe that patisiran is a safe and effective treatment option with a novel mechanism of action that should be approved to slow the decline in functional capacity and reduce symptoms in patients with ATTR cardiomyopathy.

This is the agenda for the rest of our presentation. Dr. John Berk will discuss the unmet need. Dr. John Vest of Alnylam will present the efficacy data from the APOLLO-B study, followed by

Dr. John Spertus, who will explain the impact of patisiran on patients' symptoms and quality of life. Dr. Elena Yureneva of Alnylam will present the patisiran safety profile, and finally, Dr. Ron Witteles will provide his clinical perspective on the data.

We also have additional experts here today who are available to address questions from the advisory committee. All outside experts have been compensated for their time and travel to today's meeting. Thank you very much. I'm now going to turn the presentation over to Dr. Berk.

Applicant Presentation - John Berk

DR. BERK: Good morning. I'm Dr. John Berk, a professor of medicine and assistant director of the Amyloidosis Center at Boston University. For the past 25 years, I've cared for patients with ATTR amyloidosis and have seen the devastating impact this cardiomyopathy has on patients' health, their capacity to perform daily activities, and ultimately their quality of life. Today I'll be discussing the significant unmet need for new

treatments in ATTR cardiomyopathy.

ATTR cardiomyopathy is a progressive and debilitating disease. Misfolded TTR forms amyloid fibrils that deposit in the heart, thickening and stiffening the myocardium. As the ventricular walls thicken, diminished myocardial compliance and shrinking chamber volume limits ventricular filling and reduces cardiac output. Congestion of the lungs and body produce the symptoms of heart failure. Arrhythmias, most notably atrial fibrillation, occur due to amyloid infiltration of the electrical wiring of the atrium and ventricles.

The trajectory of ATTR cardiomyopathy is one of irreversible decline. Early in the disease, compensatory mechanisms help patients cope, but as amyloid deposition progresses, the compensatory mechanisms fail, shortness of breath and fatigue worsen, and exercise tolerance declines. Patients report a sense of aging at an accelerated rate. Patients walk less and more slowly. They perform fewer activities of daily living. Bending over to tie shoes and going upstairs to the bedroom become

overwhelming. Unable to keep up, patients disengage from their partners, family, and friends.

Ultimately, patients reach a tipping point where their decline accelerates. Cardiovascular hospital admissions become frequent and longer. Time at home is dedicated to rehabilitation activities and adapting the house layout. This trajectory of decline highlights the need for early intervention and more impactful treatments.

The median survival of ATTR cardiomyopathy ranges from 2-and-a-half to 5-and-a-half years, a natural history that's worse than many cancers. The challenge of this disease is not simply its aggressiveness, but also the growing number of patients being diagnosed mainly with wild-type amyloidosis. The growth is driven by two advances in the field. The first advance was tafamidis, a TTR tetramer stabilizer and the only drug approved for ATTR cardiomyopathy.

As these four graphs from the ATTR-ACT study show, tafamidis unequivocally alters the course of disease. The mortality benefit appeared after

18 months of treatment, with tafamidis reducing mortality of 30 months from 43 percent in the placebo arm to 30 percent among treated patients. Despite treatment, nearly a third of tafamidis-treated patients died in the 30-month treatment period, however.

As you can see in the 6-minute walk test and KCCQ figures, patients in the placebo arm showed a rapid decline in their functional capacity and quality of life, reflecting the late disease stage that characterized participants in the ATTR-ACT study in contrast to those in the APOLLO-B study. Tafamidis slowed the decline compared to placebo.

While the treatment effect may seem large, the effect is amplified by the precipitous decline with placebo, yet patients in ATTR-ACT still decline substantially by all of these metrics despite the tafamidis treatment. Real-world experience bears out these observations. Functional decline and death march on despite treatment. The course of these patients defines the need for additional treatment options.

The second major advance, which occurred after the ATTR-ACT began, was the development of technetium scintigraphy as a simple non-invasive test to diagnose ATTR cardiomyopathy. The normal heart does not take up technetium tracer, whereas cardiac uptake that is equal to or greater than bone is seen in patients with diagnostic grade 2 or grade 3 scans.

This simple non-invasive imaging test has been rapidly adopted worldwide in recent years. It has effectively replaced cardiac biopsy, which was required to make the diagnosis prior to and during the era of the ATTR-ACT study. Because of this, more patients than ever are being diagnosed. In addition, disease progression is slower than in the past because patients are now diagnosed at earlier stages of the disease, but the chronic erosion of functional capacity and health is still a serious problem.

In summary, there's a high unmet need for more treatment options in ATTR cardiomyopathy. ATTR cardiomyopathy steadily robs patients of their

health, and the problem is growing with the rising number of new diagnoses. Tafamidis is the only approved therapy. The drug slows the course of disease, but patients continue to decline. Patients want to maintain their functional capacity and a good quality of life. In fact, patients often place as much or more value on their quality of life than longevity.

In the absence of new treatment options, we're left watching our patients decline. We need additional therapies, one with different mechanisms of action than TTR stabilization. In combination with early intervention, we must strive to stop disease progression and preserve functional capacity and quality of life; to settle for less means that we accept continued irreversible decline.

TTR is the disease-causing protein in ATTR amyloidosis. In hereditary ATTR amyloidosis with polyneuropathy, we know that suppressing levels of TTR result in the best outcomes. This is how patisiran works. I've cared for hundreds of

patients with hereditary ATTR polyneuropathy treated with patisiran for more than 8 years, many with concurrent cardiomyopathy. The impact of patisiran on their health and quality of life has been truly life-changing, and now with the APOLLO-B results, I firmly believe that patisiran, a TTR gene silencer, can address the high unmet need for patients with a ATTR cardiomyopathy.

Thank you. I'll now turn the presentation to Dr. John Vest.

Applicant Presentation - John Vest

DR. VEST: Thank you, Dr. Berk, and good morning. I'm John Vest, senior vice president at Alnylam, where I oversee clinical research for our TTR amyloid programs. Today, I'll be sharing the efficacy data from APOLLO-B.

APOLLO-B enrolled 360 patients with ATTR amyloidosis with cardiomyopathy. Patients were randomized 1 to 1 to patisiran or placebo and were treated for 12 months in the double-blind period. With regard to endpoints, one of the most important things to patients with this disease is how they

function and feel, so the 6-minute walk test assessing functional capacity and the Kansas City Cardiomyopathy Questionnaire assessing patient-reported health status and quality of life were identified as clinically relevant assessments for the primary and for secondary endpoint.

They were rigorously ascertained with a high degree of data completeness, and although this study was not designed to assess outcomes, secondary composite endpoints of death and hospitalization were included, and we were able to ascertain vital status for 100 percent of patients on the study. And finally, we assessed exploratory endpoints, including commonly used cardiac laboratory parameters, as well as clinically relevant assessments of disease progression and cardiac imaging parameters. After 12 months, patients entered an ongoing open-label extension, where all patients received patisiran.

APOLLO-B enrolled a global ATTR amyloidosis population and includes patients reflective of the United States population with this disease.

Baseline demographics were similar between the patisiran and placebo groups. The median age across groups was 76, most patients were male and white, and patient distribution was generally well balanced across regions.

Overall, baseline disease characteristics indicated a wide range of disease severity; however, the study focused on the patients reflective of the current ATTR amyloidosis population. Thus, patients were, on average, identified earlier in the disease course compared to previous studies. Disease characteristics were balanced between treatment arms. Eighty percent of patients had wild-type disease, 20 percent were hereditary, 25 percent of patients in either group were receiving tafamidis at baseline, and most patients had NYHA class II heart failure symptoms.

With this background in mind, I'll now turn to the primary study results supporting efficacy. APOLLO-B met the primary endpoint of 6-minute walk test, but first to contextualize the results, it's important to recognize that for healthy adults in

this age group, 6-minute walk test distance is expected to decline by 5-to-6 meters per year just due to normal ages. In APOLLO-B, the decline observed in the placebo arm of 21 meters was 3-to-4 times its expected age-related decline.

In contrast, the smaller decline of 8 meters in the patisiran arm represents a 62 percent reduction in the rate of decline compared to placebo and is comparable to the expected age-related decline in healthy adults, indicating relative stability of functional capacity in patisiran-treated patients. At month 12, the median difference between patisiran and placebo was 14.7 meters with a p-value of 0.016, a result that was consistent across multiple sensitivity analyses, confirming the robustness of the data.

Importantly, as shown here, the treatment effect observed during the double-blind period has been maintained on the open-label extension up to two full years, demonstrating ongoing preservation of functional capacity, and looking at the placebo arm, there's evidence of a treatment effect with

patients demonstrating relative stabilization of functional capacity after crossing over to patisiran on the open label.

For KCCQ, similar to what we saw for 6-minute walk test, placebo-treated patients showed clear worsening of 3.4 points over 12 months, while in contrast, the increase of 0.3 points in the patisiran arm indicates clinical stability in health status and quality of life. At month 12, the mean difference was 3.7 points with a p-value of 0.04.

Importantly, KCCQ results were also robust across multiple sensitivity analyses. Of note, the favorable effects on KCCQ were consistent across all KCCQ domains and in the clinical summary score. The two-year data on KCCQ mirror what we showed for 6-minute walk tests. Collectively, the results underscore the ongoing meaningful preservation of health status and quality of life through 24 months with continued patisiran treatment.

Now, having reviewed the primary efficacy results, I'd like to focus on several key topics.

We'll start with a discussion of efficacy in subgroups. For both 6-minute walk tests and KCCQ, we see a treatment effect of patisiran compared to placebo that is generally consistent across subgroups of baseline demographics. In subgroups of female or black patients, the N's are very small with wide confidence intervals. Likewise, the treatment effect was also generally consistent across the spectrum of baseline disease characteristics.

I would like to specifically focus on the treatment effect in patients on background tafamidis. In assessing the results in the subgroup on background tafamidis, which are shown here, in comparison to patisiran monotherapy and to the overall study population, it's important to note that this was a small subgroup with only about 45 patients per arm. The treatment effect for both 6-minute walk test and KCCQ was less than what was observed with patisiran monotherapy, but the confidence intervals are wide and overlapping.

With background tafamidis, a muted decline

in the placebo group over the 12-month, double-blind period may have limited the ability to detect potential patisiran treatment effect on clinical endpoints. Importantly, the pharmacodynamic effect of lowering transthyretin was the same with and without background tafamidis, but overall, a treatment effect for patients on background tafamidis was not established on APOLLO-B.

Next, we'll look at mechanistic data that provides support for the primary efficacy results in APOLLO-B. Patisiran reduced serum transthyretin by greater than 85 percent, which is the fundamental pathogenic protein. This result is consistent with the drug's well-described pharmacodynamic profile and is comparable to the transthyretin reduction observed on the original APOLLO study. Of note, the pharmacodynamic effect was highly consistent across all subgroups.

Looking at NT-proBNP, which is an important cardiac laboratory parameter in ATTR amyloidosis, we saw a beneficial effect with patisiran compared

to placebo, with the placebo group showing steady worsening, while patisiran substantially reduced this decline, a difference that was nominally significant. With troponin I, a commonly used laboratory marker of myocardial injury, we see a similar pattern, with patisiran demonstrating a nominally significant benefit compared to placebo.

The biomarker results are complemented by echocardiographic assessments of cardiac structure and function, shown here, where patisiran again demonstrates a favorable treatment effect. In contrast to the expected increase in LV mass seen on the placebo arm, reflecting ongoing amyloid deposition, patisiran patients demonstrated stability in LV mass, consistent with the suppression of amyloid deposition, which was in turn accompanied by a substantially smaller increase in global longitudinal strain compared to placebo, which is an important measure of cardiac function in this disease, and stable or slightly improved LV stroke volume.

These results were all nominally significant

and suggest a beneficial effect on disease pathophysiology, linking the mechanism of action of patisiran, reducing the amyloidogenic protein to the observed clinical improvements on APOLLO-B. The results for technetium scintigraphy imaging further supports this link [indiscernible]. As Dr. Berk explained, this has become a standard in the field for diagnosing ATTR cardiomyopathy.

These results reflect a prespecified analysis from a planned substudy at select sites and were analyzed by blinded readers at a central lab. In the placebo arm on the right, at baseline, it's expected that patients were all Perugini grade 2 or 3, and the vast majority remain unchanged at the end of the 12-month, double-blind period, with no patient demonstrating improvement. In contrast, on the patisiran arm, in the left-hand panel, by month 12, 38 percent of patients had improved by at least one Perugini grade. Of specific note, 5 patisiran-treated patients improved to Perugini grade 0 or 1, which is below the standard threshold grade for diagnosis of ATTR

amyloidosis.

Next, we'll look at the impact of patisiran on outcomes of mortality and hospitalization. It's important to note that the study was not designed for outcomes, and no secondary composite outcomes endpoints were met, as was described in the briefing document. Given the short duration of the 12-month, double-blind period, an analysis that includes data from the open-label extension, after all patients had completed month 24, which are shown here, provides a more robust assessment of outcomes.

The data reflect patients' overall experience in the study, including the randomized treatment and the double-blind period, plus patisiran treatment in the open-label extension. The composite outcome data of all-cause mortality, all-cause hospitalization, and urgent heart failure visits, shown on the left, as well as the analysis of all-cause mortality, shown on the right, are reassuring and indicate no detrimental effect of patisiran. The apparent separation of the

composite outcome endpoint and all-cause mortality curves between the randomized treatment groups and the open-label extension suggest a beneficial trend with longer follow-up and accumulating events.

Corroborating the results from APOLLO-B, similar results and outcomes were observed in a post hoc analysis of safety data from the original APOLLO study in hereditary ATTR polyneuropathy, which is shown here, which is further reassuring that there's no detrimental effect of patisiran, and collectively the outcomes results across two studies suggest favorable trends.

Given that we have two studies of patisiran and fundamentally the same rare disease, we took the opportunity to increase the number of events for analysis by pooling mortality data from the double-blind periods of APOLLO and APOLLO-B, shown here. We see a hazard ratio of 0.43, and the upper bound of the 95 percent confidence interval is 0.94, which convincingly rules out harm.

Having reviewed the key efficacy results and supporting data, I would now like to focus on

additional analyses underscoring the clinical meaningfulness of the primary efficacy data. To get at this, we first considered what constitutes a minimal clinically important difference for 6-minute walk test, and it's important to recognize that based on published data, MCIDs for 6-minute walk tests are highly context dependent.

This slide summarizes learnings from a systematic literature review performed. We're showing results for all studies that reported an anchor-based MCID for 6-minute walk test. What's first apparent is that 6-minute walk test MCIDs vary widely across different underlying diseases, underscoring the need to think about the MCID in the context of the specific disease being studied. Important to this point, there is no established MCID for ATTR cardiomyopathy, and literature further establishes that MCIDs for 6-minute walk tests are dependent on specific characteristics of the patients being studied.

Importantly, increased age is associated with lower MCIDs. This is illustrated here by the

red highlights that denote the studies of patients with an average age greater than 70 years. This is particularly relevant for the APOLLO-B population who are in their mid to late 70s or older, and this makes biological sense. As patients age, smaller changes are more meaningful. A change that might not be impactful for a healthy and active 50 year old may indeed be meaningful to a patient in their late 70s or 80s, who may have more limited functional ability or daily goals. Other factors, including baseline functional status, may also have substantial impact on what the patient perceives as meaningful.

Accordingly, we derived thresholds for meaningful change in 6-minute walk tests for the current ATTR cardiomyopathy patient population using KCCQ data from APOLLO-B as an anchor, which conforms with recent FDA outcomes assessment guidance. Indeed, the KCCQ meets all five requirements outlined in this guidance.

The KCCQ includes assessments of physical functioning, which is what 6-minute walk test

measures. It has well-established thresholds for meaningful within-patient changes based on the Seminal 2005 publication by Spertus, et al. The questionnaire is plainly understood by respondents. Changes in KCCQ correlate with changes in 6-minute walk tests, and the KCCQ is assessed at the same time points as the 6-minute walk test.

Our methodology for driving an MCID is shown on this slide. We categorized the median 6-minute walk test change observed on APOLLO-B, shown on the Y-axis, across three well-established categories of KCCQ change, shown across the bottom of the figure. Study patients across both treatment groups, who showed a small-to-moderate clinical deterioration based on their KCCQ scores worsening by 5 to 10 points, are shown in the left-hand bar. Their median change in 6-minute walk test distance was negative 12.8 meters.

We did the same for patients who were considered stable based on changes in KCCQ that were less than 5 points in either direction. They're represented here in the center, with a

median 6-minute walk test change of negative 5.9 meters. Finally, on the right, we see patients who showed a small-to-moderate improvement in KCCQ by 5 to 10 points. Their median 6-minute walk test distance improved by 2 meters.

To determine the MCID, we compared the 6-minute walk test value in patients with stable KCCQ with a small-to-moderate improvement, which yields an MCID for improvement of about 8 meters, or to those with a small-to-moderate decline, which yields an MCID for decline of approximately 7 meters. We then used these MCIDs to contextualize the observed 6-minute walk test treatment effect on APOLLO-B.

Here, we're showing the primary assessment of MCID outlined on the previous slide using KCCQ Overall Summary Score as the anchor, as well as MCID generated as a sensitivity analysis using the KCCQ physical limitations domain score as the anchor. I would note that the physical limitations domain assesses patients' reported ability to execute physical activities, including high

cardiometabolic demand activities such as walking and climbing stairs. And then for comparison, on the bottom of the figure, we're showing our 6-minute walk test median estimate of 14.7 meters and the 95 percent confidence interval.

You can see that regardless of which anchor we consider, our median treatment effect of 14.7 meters falls above the MCID. Importantly, the results collectively suggest that the median treatment effect corresponds to a difference in functional capacity that the majority of patients would find clinically meaningful.

In considering clinical meaningfulness of the benefit on functional capacity, we next look at results across a spectrum of treatment-effect thresholds for 6-minute walk test, including thresholds reflecting the MCIDs we have discussed, as well as change of 30 meters in either direction, and we consistently see that the worst outcomes, shown on the left, always occurred more frequently in placebo, and the best outcomes, shown on the right, always occurred more frequently in

patisiran. For example, if we consider a threshold of 30 meters, patisiran-treated patients were 40 percent less likely to decline by this magnitude and were twice as likely to improve by this magnitude. Of note, results for these larger thresholds are nominally significant.

We further considered clinical meaningfulness by assessment of disease progression, which is, of course, of high importance to physicians and patients. There are a number of tools that physicians use to track progression, and data from APOLLO-B allows us to look at the impact of patisiran on several of these clinically important parameters.

On the left is data on New York Heart Association class. First, you can see that a high proportion of placebo patients demonstrated worsening. In just 12 months, almost a quarter of placebo patients worsened by at least one NYHA class. This is a high bar clinically and underscores the relentless nature of this disease. And importantly, we see that the proportion of

patients who progressed on NYHA class was substantially low among patients treated with patisiran compared to placebo.

Complementary data looking at progression based on ATTR amyloidosis disease stage showed very similar results. Progression is common among placebo-treated patients, and substantially fewer patisiran-treated patients demonstrated worsening by this widely accepted and clinically used biomarker-based disease staging system, which is based on NT-proBNP and eGFR. These are both well-recognized clinical classification systems, and for both, patisiran prevented at least a full-class deterioration in 10 percent of patients, which is clearly a clinically meaningful effect.

This difference can also be assessed as an odds ratio. Here, we see that the odds of progression, based on New York Heart Association class and ATTR disease stage, are both approximately 40 percent lower in patisiran-treated patients compared to placebo, results that are nominally significant.

Now, to continue the discussion of clinical meaningfulness, I would like to turn the presentation over to Dr. John Spertus, who developed the KCCQ. Dr. Spertus will talk about the clinical interpretation in meaningfulness of the APOLLO-B KCCQ results.

Applicant Presentation - John Spertus

DR. SPERTUS: Thank you very much for the opportunity to present. My name is John Spertus. I'm a cardiologist in Kansas City, who's devoted his entire academic career trying to improve the patients' [indiscernible], of cardiovascular practice, and towards that end developed the Kansas City Cardiomyopathy Questionnaire.

In deference to Dr. Butler's request about my financial relationships with Alnylam, I have served as a paid consultant in preparing for this presentation today. My travel and hotel will hopefully be reimbursed, and then after this meeting, I will have no further interest or involvement in the outcome of the decision from this particular case before you today. But I do

license the KCCQ, and should they choose to use it in other studies, may receive a licensing fee from that to continue to support its development and evolution.

To orient us, again, to what we seek to do as cardiologists is, fundamentally, when we treat patients with heart failure, we're trying to prevent further progression of the disease so that they can live longer, and we're trying to make them feel better by improving their symptoms, function, and quality of life. And in fact, from patients' perspective, this is often what they care most about and why they come to us for treatment in the first place.

To help better quantify the health status of patients with heart failure, I developed the Kansas City Cardiomyopathy Questionnaire, which came from discussions with patients and providers to try and understand what is most important to patients with heart failure, and it has 23 items that capture those domains of physical function, symptoms, interaction with friends and family, and quality of

life. The symptom frequency and severity items can be grouped together to create a total symptom score that can be combined with the physical limitation score in order to create essentially the equivalent of a New York Heart Association classification for patients' perspective called the clinical summary score. Then what I like, and what was the primary focus of APOLLO-B, was the overall summary scale, which seeks to capture the totality in which the heart failure syndrome is impacting patients' lives.

Importantly, this represents the patient's perspective of their heart failure, and it seems to be applicable to all types of heart failure regardless of their etiology, as the mechanism of heart failure is often opaque to patients, and they are only aware of the symptoms that they experience and the functional limitations associated with those symptoms. It has a tremendous amount, over 25 years of work, trying to establish its validity, reliability, and responsiveness, as well as developing very clear threshold for clinically

important change, so much so that both the device and drug branches of the cardiovascular divisions of FDA have qualified it as a clinical outcome assessment.

Now, Dr. Vest has reported the mean difference in scores in the APOLLO-B study between patisiran and placebo-treated patients, both overall and in the monotherapy group, and on this slide, I'm reporting the mean treatment difference between groups in a range of cardiovascular studies of different types of interventions, many of which we believe improve the health status of our patients. And what's inherently challenging about interpreting mean treatment effects is highlighted in this graphic.

When patients are treated, some will get much better, indicated as a green caricature, and some will get worse, demarcated in red. And when we report the mean difference between groups, we are averaging the patients who got better with the patients who got worse, creating an amalgamation of somebody with a green head, yellow body, and red

legs; and yet, obviously no patient has that blended characteristics of outcomes. I think if the question before you is to understand the clinically meaningfulness of the observed changes in APOLLO-B, then it's very important to think about the proportion of patients who got better or who got worse.

This summarizes the data from APOLLO-B looking at the KCCQ, and it turns out that patients who deteriorated by 5 points or died was much more common in the patients treated with placebo than with patisiran, and conversely, the patients who improved by 5 or more points was much more common in the patisiran-treated than the placebo-treated patients.

Now again -- and Dr. Stockbridge challenges us on this -- this is contingent on is a 5-point change clinically meaningful? So I'd like to really highlight what a 5-point change means. Let us assume on the 23-item questionnaire that nothing changes but the fatigue and the shortness-of-breath items on total symptom scale in the KCCQ, and if a

patient starts out with having fatigue multiple times a day and progresses a year later, or at your next visit, to only have it a couple times per week, I believe clinically we would think that they were better, and yet that would only increase the overall summary score by 2 points.

If their shortness of breath also went from daily to a couple times a week, that would only add another point. And if both their fatigue and their shortness of breath bothered them less, from moderately to slightly bothersome, that adds only a point each such that when you compare a patient over time from the red to the green X's on this response, that is a 5-point difference, which I think most of us would intuitively feel was a patient who got better from the last time that we saw them, and that supports an intuitive sense about what a 5-point change means.

To further leverage the APOLLO-B data, we looked at the patients who had daily symptoms of fatigue and who at 12-months follow-up reported less than weekly, and we compared these categories

for both the severity of fatigue, as well as the frequency and severity of shortness of breath, and these data are shown here showing that substantially more patients went from daily to weekly, or less, fatigue or shortness of breath if treated with patisiran, and that the severity of their condition improved more in those treated with patisiran than placebo. Now, this is just a representative example, but if you look across all of the items on the KCCQ, essentially all of them favor a greater improvement in the patisiran-treated patient than in the placebo-treated patients.

In summary, I believe that the KCCQ is an extremely well-validated, patient-reported outcome with well-established thresholds that relate change in score to clinical change in heart failure status; that the average treatment effect of patients treated with patisiran in APOLLO-B is comparable to other heart failure drugs that help patients feel better, and most importantly, patisiran has a clinically meaningful impact on

improving individual patients' health status and quality of life. Thank you so much for the opportunity to present, and I now would like to turn it over to Dr. Yureneva to talk about the safety profile.

Applicant Presentation - Elena Yureneva

DR. YURENEVA: Thank you, Dr. Spertus.

I'm Dr. Elena Yureneva, and I'm the executive director and head of Medical Safety and Risk Management at Alnylam. I'll be reviewing the safety results.

Across the double-blind and open-label extension parts of APOLLO-B, 347 patients have been treated with patisiran for up to 43 months. The safety profile in APOLLO-B is consistent with the previously established in-clinical studies and the postmarketing experience. Overall, patisiran was well tolerated. Most adverse events were mild or moderate in severity. A similar rate of severe adverse events, serious adverse events, and adverse events leading to study drug discontinuation were reported in both groups.

More deaths occurred in the placebo arm versus the patisiran arm, and we will discuss them shortly. The adverse events more commonly observed on patisiran than placebo were known adverse drug reactions for patisiran: infusion-related reactions, arthralgia, and muscle spasm. The majority of these adverse drug reactions were mild in severity, transient, and did not lead to drug discontinuations. None of these events were reported as serious.

The safety profile was comparable between subgroups, including patients who were on patisiran monotherapy or background tafamidis. These are the most common serious adverse events observed. Serious events reported in 2 percent or more patients in either group included cardiac failure; atrial fibrillation; AV block complete; syncope; and amyloidosis. None of these serious adverse events were considered treatment related. Events were similar in frequency within the two groups and consistent with what is expected in this population.

Safety analysis included deaths on study as well as deaths that occurred in patients after they withdrew from the study. During the double-blind period, 5 patients in the patisiran group and 9 patients in the placebo group died. No deaths were considered related to study drug, and all were consistent with what's expected in this population.

Based on patient population, the route of administration, and the mechanism of action of patisiran, several potential areas of interest were evaluated in depth. Cardiac events were of particular interest due to the patient population. Looking into specific cardiac adverse events and serious adverse events, no safety concerns were identified, and the types of cardiac events observed were consistent with the natural history of the disease. The incidence of cardiac events in the patisiran group was similar or lower to that in the placebo group.

Infusion-related reactions can occur during the administration of lipid-containing products and are among the most common adverse events for

patisiran. As per current label, all patients received premedications to reduce incidence and/or severity of these reactions. All patisiran infusion-related reactions were mild or moderate in severity, and none were reported as serious. Only one patient discontinued the study due to a mild infusion-related reaction. As expected, symptoms were more common earlier in the course of treatment, and there was no evidence that symptoms increased in frequency with repeated doses.

TTR lowering is associated with concomitant reduction in vitamin A, therefore, there is a theoretical risk of vitamin A deficiency and associated ocular manifestations, although vitamin A can be distributed into tissues through other mechanisms. All patients are recommended to take a daily allowance of vitamin A. In case of vision-adverse events, patients were referred to an ophthalmology consult.

All ocular adverse events in the APOLLO-B study were mild or moderate in severity and, overall, consistent with the ocular symptoms and

eye disorders that are frequently reported in the general population of this age. No evidence of vitamin A deficiency has been observed in clinical trials or in the postmarketing setting.

There was no change in the long-term safety profile between the double-blind and open-label extension period, with events continuing to be consistent with those expected in this population. In summary, patisiran was well tolerated and demonstrated an acceptable safety profile that was unchanged and consistent with that previously established in the polyneuropathy population, where we have five years of postmarketing experience and over 8500 patient-years of exposure worldwide.

The safety profile was comparable between subgroups, including the patisiran monotherapy and background tafamidis groups. Primary safety considerations included infusion-related reactions, which were well managed by premedications, and there was no evidence of vitamin A deficiency, including ocular manifestations. Thank you. I'll now turn the presentation over to Dr. Witteles to

discuss his clinical perspective.

Applicant Presentation - Ronald Witteles

DR. WITTELES: Good morning. My name is Ronald Witteles, and I'm a cardiologist and the founder and co-director of the Stanford Amyloid Center, one of the nation's largest multidisciplinary amyloid centers. Over the past 16 years, I've cared for many hundreds of patients with ATTR amyloidosis. I've seen firsthand the unrelenting loss of function and worsening symptoms that can impact nearly every aspect of their lives.

As you've heard, although there have been revolutionary changes in the field, our treatment options are still quite limited. I believe we need to continue to strive to do better for our patients, and it's in that context that I'm excited to be here today to share my clinical perspective on patisiran as an important treatment option for patients with ATTR amyloid cardiomyopathy. APOLLO-B meeting its primary and secondary endpoints is of course crucial as we think about patisiran as a treatment option for patients;

however, in weighing the impact of the results, I feel it's important to first step back and think about the data holistically.

Patisiran profoundly suppresses production of transthyretin, the disease-causing protein, by more than 85 percent. This large drop in the circulating precursor leads to a fundamental altering of disease progression. We can measure a sequence of meaningful improvements in the clinically relevant markers of the disease following this rapid suppression. They start with favorable effects on the clinically important cardiac biomarkers, NT-proBNP and troponin. Both of these markers have been consistently correlated with disease outcomes and, indeed, NT-proBNP levels are an integral part of the two main staging systems used in the disease.

We similarly see a favorable impact on imaging parameters of cardiac amyloid deposition and on cardiac structure and function. These favorable biomarkers and imaging parameters, which directly follow from the mechanism of action, are

then further reflected on the observed clinical benefits on physical function that's measured by a 6-minute walk test distance and with patient-reported improvements in symptoms and quality of life. Whether we look at validated biomarkers, imaging parameters, or clinical manifestations, patisiran has favorable effects on the very methods by which patients are assessed clinically and monitored in the real world.

Patisiran has shown benefit across each and every one of these elements with remarkable consistency, and it's particularly impressive to see such consistency of benefit in just 12 months. In considering the results from APOLLO-B, I also look at it through the lens of the results of the original APOLLO study, as was highlighted earlier in the presentation.

Fundamentally, we're really talking about a single disease in which the same protein misfolds and deposits in one tissue or the other, leading to organ dysfunction. In APOLLO, this same drug led to a dramatic reduction in neurologic progression,

and now with APOLLO-B, a prospective trial specifically targeting the cardiac manifestations, has shown an unequivocally favorable effect on the disease course.

Of course, more important than what I think is what my patients want, and time and time again, patients say that their quality of life is their most important goal of therapy and what they're most afraid of losing. Now, don't get me wrong; longevity is often important to them as well, but for most patients, death is actually not the most feared outcome. My patients with the disease, who are most commonly in their 70s or 80s and who often have other comorbidities, know that they aren't going to live forever. They're not training for their next marathon. What they want is to be comfortable with their activities of daily living and activities that matter to them, taking a walk with their spouse, or ambulating around their home, or spending time with their grandchildren.

By the time a patient starts therapy in this disease, most already have substantial limitations

due to age, other comorbidities, or the progression of the disease itself. For such patients, even what a healthy 50 or 60 year old might consider a small delta in their exercise tolerance or quality of life can be highly meaningful and life-altering. As I review the data from APOLLO-B, I see important benefits on both exercise capacity and quality of life, which speak directly to the goals of treatment that I know are most meaningful to my patients.

So what does that data show? Well, from my vantage point, I see clear evidence that patisiran fundamentally alters the progression of a disease, which is otherwise characterized by an inexorable decline. This is true whether we're looking at objective markers such as 6-minute walk test and ATTR disease stage, or invalidated subjective markers such as KCCQ and New York Heart Association class. Each of these tells a remarkably consistent story that patisiran therapy leads to a fundamental alteration in disease progression.

Being treated with patisiran rather than

placebo for one year saved patients 2-to-3 years of typical age-related decline on 6-minute walk distance. When you're talking about a patient population who already has significant limitations, the clinical importance for patients is clear. And the benefit of patisiran becomes even more evident to me when I look at the two-year data, where the 6-minute walk test results remain relatively stable on patisiran, and this stability which mirrors the expected age-related decline in healthy adults would definitely be meaningful to my patients.

And while we don't have long term placebo data in this study, given the crossover to open-label treatment at 12 months, from my clinical experience, a steady decline would be expected in the absence of treatments. That's illustrated here by the dashed line that extrapolates the placebo patients' decline over the first 12 months forward to year 2.

This clearly highlights why I believe that these benefits on physical function, which are already important at year 1, would only grow over

time. Furthermore, when you look at the placebo patients who receive drug and seem to be starting to benefit, they haven't caught up to the original patisiran-treated patients who started drug 12 months earlier, which further reinforces the need to treat early before disability accumulates.

This data is mirrored looking at the important secondary endpoint of change in patient-reported quality of life as assessed by KCCQ. For patient-reported, quality-of-life measures to essentially remain constant in patisiran-treated patients throughout 24 months, of what would otherwise be disease progression, is really important.

This is an outcome that I know would be meaningful to my patients, and again is very different from what I would otherwise expect in this disease. To this point, I again want to draw your attention to what we would anticipate happening to the placebo patients if they had not started receiving patisiran on the open label, represented by the dashed line. I'd once again

note that one can reasonably project that the treatment benefit would continue to grow over time.

Now, I can think of many patients in my clinic with whom I would hope to have the option to discuss patisiran as a treatment option. The specific-use cases I can see include first-line monotherapy, and an obvious example here would be a patient with mixed phenotype disease, meaning a patient who has both cardiomyopathy and polyneuropathy from ATTR amyloidosis for whom patisiran would be an excellent option. In addition, a patient with cardiomyopathy predominant disease could very rationally and reasonably choose patisiran as solo first-line treatment, particularly if they're considering the totality of the data from all ATTR amyloidosis clinical trials to date.

Another example is a switch for patients progressing on tafamidis. Currently, there's simply no alternative treatment option available for such patients as they continue to progress. And finally, I feel this could be considered as an

add-on to tafamidis following an informed discussion. And while I acknowledge that we don't yet have clear data to guide this question, it is a reasonable consideration for patients, considering the favorable safety and efficacy profiles for both agents, as well as their orthogonal mechanisms of action.

In summary, ATTR amyloid cardiomyopathy is a very serious, progressive, and often devastating disease. Patients and physicians currently have only a single approved treatment option with no alternative therapies to consider, either upfront or if a patient's disease is progressing despite treatment. As you've seen throughout this presentation, patisiran has demonstrated clear efficacy as a clean safety profile and importantly works by a completely different mechanism of action from the only currently available therapy.

Patients deserve more than one treatment option, and particularly one which has such a clearly favorable ratio of potential benefits, which are very real, to potential harms which are

essentially nil. I therefore very much hope that the outcome of this committee is a recommendation for approval of patisiran for the treatment of ATTR amyloid cardiomyopathy. Thank you very much for your attention, and I will now hand the presentation back to the sponsor to take your questions.

Clarifying Questions to Applicant

DR. BUTLER: Thank you very much for your presentations.

We will now take clarifying questions for Alnylam Pharmaceuticals. Please use the raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon again after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge

the end of your question with thank you and the end of your follow-up questions with, "This is all for my questions," so we can move on to the next panel member. We will open this session up now for clarifying questions.

So while the panel members are going to this, may I take the liberty of asking the first question to Dr. John West, please?

MR. SLUGG: Yes. Please, Dr. Butler, go ahead. My name is Andrew Slugg. I'm the head of Global Regulatory Affairs, and I'll be moderating the session for the sponsor, but please address your question.

DR. BUTLER: Great. Javed Butler. My question is, your primary endpoint of 6-minute walk test, did you in the beginning of the trial have a hypothesis of how much improvement is expected to power the study? And the anchor analysis that was performed, was that also prespecified whether to use the KCCQ-OS or KCCQ-PLS, or were these post hoc decisions to understand the data better?

MR. SLUGG: Dr. Butler, we have the benefit

of my colleague, Dr. Nancy Silliman, who heads up our data science and statistics group, and she'll address your questions for you.

DR. SILLIMAN: Nancy Silliman, Alnylam. At the time we designed APOLLO-B, there was limited data. Unfortunately, ATTR-ACT was the only pivotal study that has been conducted in ATTR cardiomyopathy with 6-minute walk test in KCCQ. So we assumed for our APOLLO-B monotherapy subgroup, the largest subgroup in our trial, that we would see similar changes in 6-minute walk test as we're seeing in ATTR-ACT at 12 months.

We expected about 30 percent of patients to be on background tafamidis. Unfortunately, there was no data to inform the effect size of combination therapy, so we assumed it would be 60 percent of monotherapy due to the expected reduced decline on placebo as those patients were receiving tafamidis. So the sample size of 300 provided 90 percent power to detect a 29-meter difference, and I'll note that this was not meant to be an MCID; it was simply based on what we

understood from ATTR-ACT.

Of course, with the change in the patient population over the last several years, earlier diagnosis and cardiologists knowing better how to care for patients, we see a lesser decline on placebo and lesser absolute treatment difference, but we see a very similar relative treatment difference. So we see 62 percent slowing of decline compared to placebo in APOLLO-B, which is very similar to the 58 percent that they saw on ATTR-ACT.

I'll just note that KCCQ was powered similarly, and we see a similar relative treatment effect as expected. And importantly, we see stability in both 6-minute walk test and KCCQ in patients receiving patisiran in APOLLO-B for 24 months.

In terms of the MCID methodology, we had only spoken with the FDA about the p-value expectations. We have not talked about a specific threshold, so that was a post hoc analysis, and we took the opportunity to use the patient-reported

outcome that we had available in APOLLO-B, so we used the KCCQ to incorporate the patient voice to calculate the anchor.

If I could have CM-12, please? Thank you. I would like to walk you through the guidance document and how KCCQ Overall Summary Score as an anchor conforms to the FDA guidance. It meets all five criteria that they lay out. On the left of this table, you see in italics direct quotes from the FDA guidance, with a little bit of bolded information from Alnylam just to clarify some concepts, and on the right, you see how how we believe that KCCQ-OS meets these criteria.

The first concept that's required for an anchor for an MCID analysis is ideally the concept assessed by an anchor variable. Here, the KCCQ-OS should match or be inclusive of the concept of interest -- here, physical functioning -- being assessed by the COA based endpoint; here, 6-minute walk test. And KCCQ-OS, as Dr. Spertus described, does incorporate assessment of physical functioning.

The second criteria is that an anchor should have a well-justified definition for meaningful change or for meaningful increments. Again, as Dr. Spertus described, they're well-established thresholds from the Seminal Spertus et al., 2005 paper, showing changes less than 5 are considered stable change. Improvements of 5 to 10 are considered a small-to-moderate improvement, and declines of minus 5 to minus 10 are considered a small-to-moderate decline.

The third criteria is that an anchor should be plainly understood by respondents in the context of use, and this again was confirmed as part of the development of the KCCQ tool. The fourth criteria is that differences in COA scores should be related to differences documented by one or more anchors, and, again, as part of the validation of the KCCQ tool, they saw a significant correlation of 0.37 for 6-minute walk test. Then finally, the fifth criteria is that selected anchor should be assessed at comparable time points to the target COA, and we did in fact in APOLLO-B assess 6-minute walk test

in KCCQ at the same study visits.

I'll note that the guidance acknowledges identifying an external data set in rare diseases can be challenging and supports the use of internal data as needed. Unfortunately, in this rare disease, ATTR cardiomyopathy, there was no external data set available to the sponsor, but we were able to use our own APOLLO-B study to use the patient voice in the KCCQ tool to help contextualize and understand the average treatment effect across the groups in 6-minute walk test.

Maybe I'll just add one other point. There is actually a precedent sNDA that was approved in May of last year in another rare disease. That was dupilumab for eosinophilic esophagitis, and there both the FDA and the applicant used a within-study anchor-based analysis to characterize the clinical meaningfulness of one of their co-primary endpoints, the dysphagia symptom questionnaire total score, and this anchor-based analysis is presented in their labeling. Thank you.

DR. BUTLER: Thank you very much. That will

be all for my question.

May I request Dr. Bairey Merz to ask her question?

DR. BAIREY MERZ: Thank you, Dr. Butler. My question is for Dr. Spertus.

As you and the sponsor elegantly demonstrated, the heart failure trials all use a mean change of the KCCQ, and yet in your presentation, you talked about a better analysis would be to use individual patient-level categorization, which starts to sound like subgroup analyses.

The FDA duty is for population health and to evaluate critically interventions for the average patient or a patient population. So what would your response be regarding this rationale and how we should consider changing your tool? You did talk about it in your JACC 2020 article, so I'm interested in those thoughts. Thank you.

MR. SLUGG: I'll turn it over to Dr. Spertus for you.

DR. SPERTUS: Thank you very much for the

opportunity to address what I think is really an important issue, and that is that my belief is that, as the FDA does, you should look at the mean difference to test with a statistical significance of an observed difference between groups. However, the real challenge is not is there a difference in the KCCQ Overall Summary Score between patisiran and placebo, but is that clinically important.

So once you define that there is a statistically significant benefit of treatment in a patient-reported outcome measure, then the next step is to put it through a clinical lens to define whether or not you think that's a clinically important difference, and that's the purpose of categorizing patients into groups of different magnitudes of clinical change, which is exactly what I had really proposed and encouraged our field to do in the JACC state-of-the-art review on interpreting the KCCQ that you referred to.

So I don't believe I've been inconsistent over time. I do think that testing the statistical significance of the continuous mean difference in

scores defines whether one group is better or not, but then if you find that it's beneficial, and you want to define is that a clinically important difference, I don't think you can glean that information by looking at the mean difference between the groups; and therefore, you have to look at the proportion of patients who change, either improve or deteriorate, by different clinical magnitudes. Thank you very much for the opportunity to address that issue.

DR. BAIREY MERZ: So Dr. Spertus, this is a secondary analysis. It is like a subgroup analysis. Would you agree with that?

DR. SPERTUS: No. I mean, I normally think about a subgroup looking at a proportion or a specific profile of patient and did they derive a different effect or not, so that it's the patient characteristic that defines the subgroup. Here, we're just categorizing the outcome, so it's not really a subgroup analysis at all. It's a way of trying to categorize a near continuous measure into more clinically interpretable buckets so we as

clinicians can understand what's the number needed to treat or how many patients would benefit by what magnitude from treatment.

So that's what we're seeking to glean from categorizing the outcome, which I think really differs than a subgroup, which is subdividing the pool of patients. All the patients are included in this analysis, but we're focusing on different thresholds of improvement.

DR. BAIREY MERZ: Thank you, Dr. Spertus.

Dr. Butler, that's all for me.

DR. BUTLER: Thank you, Dr. Bairey Merz.

May I request Dr. O'Connor to ask your question?

DR. O'CONNOR: Yes. Good morning. Chris O'Connor. I have a couple questions around the design of the trial and conduct. Number one, it seems like a large part of the trial occurred during the COVID pandemic. Could you comment on how the 6-minute walk test, and KCCQ, and drug administration were handled during the COVID pandemic?

The second question is, it appears you decided to cap the tafamidis background therapy at 25 percent -- I think that's what happened -- at the beginning of the trial. In the context of a very important and powerful therapy, I wonder why that was capped, and what did you see post-randomization in the trial of the utilization of tafamidis? And then finally, why did you limit the follow-up to 12 months?

MR. SLUGG: Let me have my colleague, Dr. Vest, address your questions.

DR. VEST: Yes. John Vest, Alnylam. So part one of this was about the trial being conducted during the COVID pandemic and, indeed, most of the patients were enrolled after the onset of the pandemic. I think your specific question was with regard to how we implemented the 6-minute walk test. All patients received the 6-minute walk test on site at their treatment center, and as we highlighted during the presentation, we had very little missing data, less than 10 percent, for both the 6-minute walk test and the KCCQ, which was also

implemented on site. Patients were able to receive treatment, either on site or at home, and we also had very few missed infusions over the course of the trial. I think all of this is testament to the patients' dedication on the study.

The next question I believe was about the the rationale for capping the background of tafamidis, and I think it's important to remember that when we began this trial, tafamidis had just been approved, and its use in the real world was not well understood. We were also enrolling a global study, and tafamidis was just becoming available in various regions around the world, so we decided to allow tafamidis on the study in regions where it was available. We did, as a practical matter, implement a cap of 30 percent, as you've highlighted. We felt that would give us some experience with the two drugs together in this rare disease and, again, allow us to enroll populations reflective of patients around the world.

With regard to the use of tafamidis during

the study, as specified in the protocol, patients who came in on background tafamidis were encouraged to remain on tafamidis for the duration study, and there was almost no discontinuation of tafamidis during the study. The other question might be around drop-in of tafamidis, and there was very low drop-in. We had 8 patients total. It was balanced between treatment arms; 5 patients dropped in on the patisiran arm and 3 patients dropped in on the placebo arm over the course of the double-blind study.

Oh sorry. The last part of your question was around the 12-month duration of the study. To get this, we need to go back to the unmet need that Dr. Berk highlighted in his presentation, that preventing accumulation of disability, preserving function, and maintaining health status is incredibly important to these patients, and this is something that the treating physicians are routinely seeing a decline despite the available therapy.

We saw an opportunity to address this unmet

need with the patisiran development program, with a medicine with a unique mechanism of action that was already FDA approved and a very similar indication. We were informed by both the APOLLO of patisiran and the ATTR-ACT study of tafamidis that we would see benefit on important assessments of how patients function and feel in a 12-month study. So we approached this with urgency -- in a rare disease where there's only one treatment option, where disease progression remains common -- to try to bring this therapy forward as quickly as possible for patients. Our approach was aligned with the FDA, and the selection of these endpoints was consistent with subsequent FDA guidance for assessments in heart failure studies. Thank you.

DR. O'CONNOR: Thank you.

DR. BUTLER: Thank you very much, Dr. O'Connor.

May I request Dr. Moliterno to ask his question?

DR. MOLITERNO: Yes. Thanks, Dr. Butler. David Moliterno, a few different questions, but

springboarding off of some from Dr. O'Connor, and maybe some simpler questions perhaps to Dr. Vest.

It has to do so with the the steroid injection, and maybe I missed it in the beginning. Did you mention what the steroid dose was that was given concomitantly to the patients?

MR. SLUGG: Ten milligrams.

DR. MOLITERNO: Ten milligrams of --

MR. SLUGG: Yes, of dexamethasone, and that's allowed to be down-titrated as patients continue to tolerate the infusions over time.

DR. MOLITERNO: Got it. Would that have been given similarly to all patients, or do you know all subjects receiving study drug and all subjects receiving placebo, or did you keep track of what percentage of patients received steroids?

MR. SLUGG: Yes. That was very important to maintaining the integrity of the trial, so we did ensure that all patients who received study drug, whether it be patisiran or placebo, received premedication regimen, including dexamethasone.

DR. MOLITERNO: Got it.

Would that have been similar for the neuropathy study? Were they getting also steroids then?

MR. SLUGG: Yes, that's correct. The premedication regimen that was used in APOLLO-B is what was used in the initial APOLLO study, and is also part of the approved labeling that's been used, in postmarketing use now, for five years.

DR. MOLITERNO: I'm just trying to see if there was any effect. During the open-label phase for that second year of patients, would they have still gotten steroids during that time?

MR. SLUGG: Yes. As part of the premedication regimen for any infusion of patisiran, we recommend the premedication regimen, including steroids, acetaminophen, and H1 and H2 blockers.

DR. MOLITERNO: Sure. No, I'm not trying to chase a rabbit trail. I'm just trying to imagine, during the open-label phase, people getting, during that next year, 17 doses of steroids. So maybe a question to to Dr. Spertus, if he knows, is there

Kansas City Cardiomyopathy-like questions for patients who have gotten multiple steroid doses over time to see if they have an impact on some of the aspects of the questionnaire?

MR. SLUGG: Sure. We'll have Dr. Spertus come address your question.

DR. MOLITERNO: Thanks.

DR. SPERTUS: It's an interesting question, and I can only speculate. It's something I've never really confronted before. We designed the questionnaire to be disease specific. I have a hard time hypothesizing how a brief euphoria from steroids would alter responses to the KCCQ, and my gut tells me that it would not influence the responses. That said, I really don't have any empirical data to confirm that.

DR. MOLITERNO: No, but I think we can speculate -- I'm not trying to push it -- they do affect psychosocial perceptions. But in addition, we know these patients have other musculoskeletal or degenerative joint things, that you wonder if recurrent doses of steroids may have other things

that may impact their quality of life. That's all.

DR. SPERTUS: So given the opportunity to speculate wildly, I would say that I wouldn't think that that would actually be much at play here. The KCCQ asks very concrete questions. I showed with fatigue and the shortness of breath, really, how much often have you been shortness of breath over the past 2 weeks, from multiple times a day to none over the past 2 weeks, and I would not think that that would -- it's really part of our effort to try and make it as disease specific as possible, and I would not think that the generic impact of steroids would have a substantial influence on that. But again, you're giving me an opportunity to speculate, and therefore I'm seizing it with great joy. Thank you.

DR. MOLITERNO: I'll look forward to a future manuscript on the topic. I have no further questions.

MR. SLUGG: Dr. Moliterno, just to underscore, patients on both arms received premedication regimens.

DR. MOLITERNO: Sure, but not on the open label in that subsequent year when we'd see --

MR. SLUGG: No. All patients have received the premedication regimens before every single dose of patisiran or placebo.

DR. MOLITERNO: But in the open label, that second year from 12 to 24 months, obviously they're receiving the drug open label, and you wouldn't expect then patients to get steroids, that they weren't getting the study drug.

MR. SLUGG: All patients were receiving patisiran the second year, and therefore they received premedication regimens beforehand.

DR. MOLITERNO: Sure. Understood. Thank you. No further questions, Dr. Butler.

DR. BUTLER: Thank you.

Javed Butler here. Just to clarify, the placebo arm premedication was placebo premedication or the study steroid?

MR. SLUGG: Yes. Let me clarify, Dr. Butler. So all patients in the study received the exact same premedication regimen at all time

points prior to each infusion of either placebo or patisiran.

DR. BUTLER: Thank you very much.

MR. SLUGG: You're welcome.

DR. BUTLER: Dr. Cella, may I request you to ask your question?

DR. CELLA: Yes. Thank you, Dr. Butler.

Could you pull up slide CO-57, please? And my question is probably for Dr. Silliman, but maybe Dr. Spertus because this was the slide that he presented. I actually have three questions.

The first one is, do you have the sample sizes for each of these groups? The second question is did you test the significance of those differences in proportion? And the third question is, did you do any sensitivity analysis with larger values such as 10?

MR. SLUGG: Yes. Let me ask my colleague, Dr. Silliman, to address your question.

DR. CELLA: Thanks.

MR. SLUGG: You're welcome.

DR. SILLIMAN: Nancy Silliman, Alnylam. The

sample sizes in the groups, we'll have to get that to you after the break. These are post hoc analyses, and we did look at the odds ratios for these responder analyses, along with confidence intervals. And you can see that there's about a 22 percent reduction in the risk of deterioration and about a 64 percent probability of having a better improvement greater than 5.

DR. CELLA: And did you look at other values such as 10?

DR. SILLIMAN: We have looked at other values. I'll have to get that to you after the break, unless we can -- I know we've looked at changes greater than 10 and less than minus 10.

DR. CELLA: That'd be great. Thank you.

DR. SILLIMAN: Okay. Thank you.

DR. BUTLER: Dr. Cella, do you have any follow-up questions?

DR. CELLA: Sorry. That's all my questions, Dr. Butler.

DR. BUTLER: Great. Thank you very much.

May I request Dr. Thadhani to ask his

question?

DR. THADHANI: Thank you. Ravi Thadhani, asking a following question. There was a commentary earlier on in the presentation certainly that the FDA had discussion with the sponsor, thought about the benefit of a single trial given this was a rare disease; and, hence, a single trial, I would imagine a strong effect size would suffice in terms of the indication. Usually when a single trial is suggested, we're looking at a pretty large effect size so that the results are convincing.

The sponsor presented data that given the age of the patients enrolled in the study, the effect sizes would have been expected to be small, especially for certain measures, namely the primary and key secondary endpoints. When we look at the trial of tafamidis, the mean ages are in the mid 70s, similar to the trial of APOLLO-B, but yet the effect sizes were 5 times greater for 6-minute walk test and about 3 times greater for the KCCQ. And I'm assuming, based on those results, the power of

the study, as was demonstrated, or as was highlighted, was created.

I would like the sponsor just to comment on just that, in terms of discussion with the FDA. Was there discussion on effect size anticipated? I would imagine there was, given the power of the study that was based on a much higher effect size; and two, given the lack of benefit among patients that did receive tafamidis. I have another question to follow up, but I'd like the sponsor to address the first one, please.

MR. SLUGG: Dr. Thadhani, I want to make sure we understand your question is essentially around the powering of the study, the assumptions that we made going into the design of the trial that you would like for us to respond to?

DR. THADHANI: I apologize. Let me make it more clear. Was there a discussion with the FDA on the anticipated effect size and the expectation with a single trial? What kind of effect size would need to be present before a single trial would suffice as a registrational study?

MR. SLUGG: No, there weren't. There weren't any specific effect sizes that were discussed with the agency. We did discuss with them clinically meaningful and statistically persuasive results, but there was no specific threshold response that was prespecified or discussed with the agency. As my colleague, Dr. Silliman, can explain, we did make certain assumptions regarding powering of the study, but those weren't necessarily part of the discussions.

Thank you. I have a follow-up question, Dr. Butler, if that's ok.

DR. BUTLER: Yes, please.

DR. THADHANI: At the beginning of this presentation, Dr. Stockbridge spoke about responder analyses and the caution thereof, as well as regression to the mean. We clearly have seen data, especially on the responder analyses. I'd like to ask the sponsor to address those two concerns that Dr. Stockbridge addressed at the beginning of this session.

MR. SLUGG: Let me ask Dr. Signorovitch to

come help address your question.

DR. SIGNOROVITCH: James Signorovitch, analysis group. To provide some context for the responder analyses that were presented and to address the opening comments, I'd like to respond to those two issues.

First, the responder analyses do tell us something new that we can't see just from looking at the mean differences between groups. It's very possible that a treatment could impact the average, but not have an effect on patients who experience more extreme changes. That is certainly biologically possible. So it's reassuring that when we look at the proportions of patients that exceed certain thresholds in KCCQ or 6-minute walk, we see that meaningful improvements or avoidance of decline occur more frequently in the patisiran group compared to placebo, and that I think adds importantly to the totality of the evidence of meaningful efficacy for patisiran.

There were also important points raised about measurement noise and error and possible

regression to the mean that could impact 6-minute walk and KCCQ, and these are factors that would occur in in any clinical trial and would impact both of the treatment groups. In fact, they would tend to dilute the power to see an effect. That's why it's important that this was a randomized, double-blinded trial for these PRO and performance-based outcomes. So the primary responder analyses give us a result that we have confidence in and help us interpret the clinical meaningfulness of the demonstrated effect.

DR. THADHANI: Thank you. And just to clarify that, those were post hoc analyses, correct? All of those were post hoc analyses?

MR. SLUGG: The threshold analyses you're referring to?

DR. THADHANI: Yes, sir.

MR. SLUGG: Yes, that's correct. Yes.

DR. THADHANI: Thank you, Dr. Butler. That's all I have.

DR. BUTLER: Thank you, Dr. Thadhani.

May I request Dr. Kasper to ask his

question?

DR. KASPER: Thank you, Dr. Butler, and thank you to the presenters for being succinct and very clear. I have one question, and that is the use of the KCCQ in the anchor analysis is interesting to me. I have not seen it done before, but I wondered if I'd missed that. I gather also that this was an ad hoc analysis as well and whether you'd discuss this with the FDA at all. So that's my question. Thank you.

MR. SLUGG: First, I'll address the second part of your question, which this is a post hoc analysis, and as we went through the review of our application, FDA has asked questions to help interpret the clinical meaningfulness of the APOLLO-B results. So as part of that exploration, we wanted to help assess and give meaning to the 6-minute walk test distance and how that impacted patients' quality of life, so we endeavored to employ this new FDA guidance to help explore that analyses. And let me have my colleague, Dr. Silliman, help address the rest of your

question.

DR. SILLIMAN: Nancy Silliman, Alnylam. We did a systematic literature review to look at MCID analyses for 6-minute walk test, and we did find that a number of those publications used multi-part questionnaires. There was one specifically that used the KCCQ-OS as an anchor. Within our trial, the KCCQ was really the only patient-reported tool that we had, so we looked at the overall summary score, which was our secondary endpoint, as kind of the primary analysis to determine MCID. And then because the physical limitations score is specific to physical functioning, which is what the 6-minute walk test measures, we used that as a sensitivity analysis.

We did also look at the clinical summary score, which you can see here in the middle, and that provides very similar estimates for the MCID. We weren't able to use any of the other domain scores because they don't incorporate the concept of physical functioning.

MR. SLUGG: Dr. Kasper, I may have

incompletely addressed your question as well. While we did explore this during the course of the review, we did share this analysis with FDA at our mid-cycle meeting, and then there were some exchanges during the course of the review in response to questions in which we explored this together.

DR. KASPER: Thank you, Dr. Butler, and that's it for me.

DR. BUTLER: Thank you, Dr. Kasper.

May I request Dr. Roy-Chaudhury to ask his question?

DR. ROY-CHAUDHURY: Yes. Thanks, Dr. Butler, and appreciate all the presentations till now. My question probably centers around slide CO-77, and I'll start off by saying that the patient perspective is obviously very important in these sorts of studies and the patient outcomes, so I do appreciate the importance that all of you have placed on that. But also from a patient perspective, it's very important as to what happens not just at 12 months, and on this slide with the

open-label extension, perhaps up to 24 months, but also what happens out at 3 years and 5 years, and that could become more and more important with the technetium scanning and the fact that we're now going to be able to identify people earlier.

So the question is, is there any data about whether the treatment line in this case continues to be flat over a longer period of time, perhaps from the cardiomyopathy patients in the APOLLO study, or is there some flattening out of the benefit?

MR. SLUGG: Sure. Let me have my colleague, Dr. Vest, address your questions.

DR. VEST: John Vest, Alnylam. The results we've presented today in ATTR cardiomyopathy, we're very encouraged by what we've seen through two full years on the study. We definitely appreciate your question about what will happen in year 3, year 4, and year 5. We don't have that experience in cardiomyopathy yet, but what we do have is very extensive experience in the peripheral neuropathy of the same disease, in hereditary peripheral

neuropathy, where we now have data out through 7 years. And what we know is that the reduction of the pathogenic protein remains entirely consistent in its suppression, and we have favorable clinical benefits on neuropathy manifestations of the disease over that same time period.

What I'd like to do is have Dr. Berk come, who actually has the experience of having cared for these patients over many years with this disease.

DR. BERK: Thank you for the opportunity to comment on the durability of effect. While we don't have longitudinal data that extends beyond 2 years for cardiomyopathy, we have extensive data in the polyneuropathy population. And I will say to you, quite bluntly, it is life-changing, absolutely life-changing. And to me, as a physician who has cared for these patients over time, it's hard to share with you exactly how satisfying it is, and I will tell you just by clinical scenarios, there's a 42-year-old woman that was just involved in a TTR gene-silencing trial, the HELIOS-A trial, and in that trial, she

has had remarkable sensory and motor nerve improvement.

The moving part of this is that at the age of 42, she's facing the time at which her mother died despite a liver transplant, she has two young children that she's hoping to mother and see through graduations, and she was so moved by the marked effect on her life, her outcome, and her ability to look forward that she had to give me a hug, and I'm not a huggable person.

I'm not exactly sure which words to use, but I will say bluntly that patisiran over time has a very durable effect, and certainly anticipate the same will be true of cardiomyopathy.

DR. ROY-CHAUDHURY: Thank you for those comments, and obviously as physicians, personal patient interaction is really important. But just as a quick follow-up question, if I may, Dr. Butler, when we're talking about longer term effects, particularly in the polyneuropathy group -- because I'm presuming there were no 6-minute walk tests, for example, in the APOLLO

study in the cardiomyopathy patients. So if you just look at the polyneuropathy data out to 7 years, were there particular groups of people where the stabilization in the outcome measures was more prominent, and also were there groups where it was not so prominent? I'm just trying to get a feel about as we look out longer term, there are certain subsets that will do well and will not do well.

MR. SLUGG: Let me have my colleague, Dr. Vest, to address your follow-up question.

DR. VEST: John Vest, Alnylam. With regard to this experience with patisiran in this closely related indication, we have seen remarkable consistency across all subgroups with regards to suppression of the pharmacodynamic effect and with the clinical assessments that are done as well. It's been quite consistent, and it's certainly not limited or accentuated in any one subgroup. Part of that is the pathophysiology of this disease is the same across all of these subgroups, all driven by the same pathogenic protein.

DR. ROY-CHAUDHURY: Thank you so much. That will be all, Dr. Butler. Thank you.

DR. BUTLER: Thank you, Dr. Roy-Chaudhury.

May I request Dr. Kovesdy to please ask his question.

DR. KOVESDY: Yes. Thank you, Dr. Butler. Csaba Kovesdy. I have two questions, really. The first one would refer to slide CO-33, the subgroup analysis with tafamidis users and non-users. Was there a statistical interaction testing conducted for this particular subgroup analysis? And as a follow-up of this regarding the mechanistic analyses, were those examined in tafamidis users and non-users separately or not?

MR. SLUGG: Let me have my colleague, Dr. Silliman, address your first question.

DR. SILLIMAN: Nancy Silliman, Alnylam. So yes, we did do subgroup by treatment interaction test, and for baseline tafamidis, the result was marginal for 6-minute walk test. The p-value was 0.06. Often a value less than 0.1 is considered significant for a treatment interaction, but given

the number of subgroups, it's also likely that it's just noise. We did not see a significant interaction with baseline tafamidis for KCCQ. That p-value was 0.59.

MR. SLUGG: And to your second question regarding any mechanistic ties in this subgroup, let me have my colleague, Dr. Vest, to address your question.

DR. VEST: John Vest, Alnylam. Most importantly, with regard to the mechanistic ties is the pharmacodynamic effect of suppressing the pathogenic protein, and we're showing that here, and you can see that the suppression of transthyretin is essentially identical in patients with or without background tafamidis.

DR. KOVESDY: I'm sorry. I'm more interested in the cardio biomarkers --

DR. VEST: Oh, oh.

DR. KOVESDY: -- and the cardiographic results. Mechanism of action, I would have expected these results, but how about the cardio biomarkers?

DR. VEST: I got you. So yes, we did look at the biomarkers and the echocardiographic parameters. There was no difference in NT-proBNP, but we saw some evidence of a treatment effect on troponin I. The echocardiographic subgroup is simply too small to have any meaningful interpretation of the data.

DR. KOVESDY: Thank you. That's all.

DR. BUTLER: Thank you very much, Dr. Kovesdy.

Can I ask a further clarifying question on this issue with interaction? This is Javed Butler. May I ask a further clarifying question related to the interaction with tafamidis? So we saw the data for KCCQ and for 6-minute walk test. Do you have the same data for clinical outcome, mortality hospitalization outcome as well, with tafamidis and without tafamidis?

MR. SLUGG: Let me have my colleague, Dr. Vest, to address your question.

DR. VEST: John Vest, Alnylam. The question is about outcomes by background tafamidis. Yes, we

do have that data, and this is an area where we do see some encouraging data in the background tafamidis group. We're showing here, first, the composite endpoint of all-cause mortality, hospitalization, and urgent heart failure visits. Patients in background tafamidis are shown on the left; patients on patisiran monotherapy are shown on the right.

You can see that in the background tafamidis group, there is a trend favoring patisiran on the composite. We don't see any separation in the monotherapy arm, but the hazard ratio is 1, and there was a lower number of events in both treatment arms, so we simply may not have followed these patients for long enough.

We also looked at mortality by background tafamidis use. That's shown here. Again, patients on background tafamidis are on the left-hand panel; patisiran monotherapy on the right, and this is from the 24-month data cut. You can see a trend favoring patisiran that is consistent both with background tafamidis and the patisiran monotherapy.

DR. BUTLER: Thank you very much.

May I request Dr. Peterson to ask his question?

(No response.)

DR. BUTLER: You're muted, Dr. Peterson.

DR. PETERSON: Sorry. Thank you very much for this presentation. I just have a couple quick questions, the first of which is, the results of the primary endpoint, as well as the primary/secondary endpoint, looked at functional measures. The importance of blinding in this double-blind trial is important. Did you assess whether patients knew which therapy they were on?

MR. SLUGG: Sure. Of course, in a trial like this, blinding is actually important. Let me have my colleague, Dr. Vest, address your question.

DR. VEST: John Vest, Alnylam. We went to great lengths to maintain the blind on this trial. Importantly, all personnel were blinded to the study treatment, and the implementation of the 6-minute walk test was required to be performed by somebody who wasn't the principal investigator or

somebody directly caring for the patients. We are confident that the blind was maintained and have no reason to believe that unblinding led to bias. I might also point to the consistency of the treatment effect that was seen on entirely objective assessments such as the cardiac biomarkers, both NT-proBNP and troponin, as corroborating the clinical assessments.

DR. PETERSON: Yes. I don't know if you directly answered my question. Were the patients themselves interviewed to ask whether they knew which therapy they were on?

MR. SLUGG: This was not an interview that we undertook, no.

DR. PETERSON: Okay.

Then the second question has to do with the follow-up questions to the tafamidis subgroup analysis. Do you have the slide that would show the biomarker data, particularly the proBNP data?

MR. SLUGG: We'll try to get that to you after the break.

DR. PETERSON: Okay. That will be all.

Thank you.

DR. BUTLER: Thank you, Dr. Peterson.

May I request Dr. Smith to ask her question?

DR. WILDER SMITH: Yes. Thank you. Ashley Wilder Smith. I have one question. If you could go to slide 31, I'm wondering if you could comment a little bit more about the subgroups focused on women and black or African American patients and what you're seeing here. I'm also wondering if you did any subgroup analysis in your open-label, follow-up portion for the subgroups that are presented on this slide.

MR. SLUGG: Let me have my colleague, Dr. Vest, to address your question.

DR. VEST: John Vest, Alnylam. The question is around the results in the subpopulations of black patients and women. Let me start first with the subpopulation of black patients on the study. While the subgroup of black patients reflects the demographics of the disease proportionally, in the context of the overall study size, this was a very small subgroup, only about 15 patients per arm.

And accordingly, there's heterogeneity between the -- I'm just going to focus in on the forest plot there -- treatment arms, as we would expect, and substantial variability in the individual clinical assessments. For both endpoints, the confidence intervals here are very wide.

We have looked at this statistically, and there's not a significant difference between the black subgroup and any other race for either of the endpoints, the 6-minute walk test or KCCQ. With that said, we are, of course, very interested in understanding these results, particularly with regard to the KCCQ.

The short answer is that we don't have a definitive explanation for the observation, but it appears to simply reflect the small subgroup being influenced by results in the small number of individual patients. For instance, there were swings 40 to 60 points in some individual patients, but most importantly in this regard, on the placebo arm, there were 4 deaths prior to the month 12 time point, so a substantial number of the overall size

of the arm is only 15 patients -- and because we don't impute data for cases -- sorry, compared to only one death on the patisiran arm prior to month 12. Because we don't impute those data, that means they're not reflected in the month 12 analysis, so what we're seeing may reflect a survivor bias.

I would note that the pharmacodynamic effect is entirely maintained, that a reduction of pathogenic protein in the black patients on the study is entirely consistent with what we see in the overall population, and the pathophysiology is the same across all races and demographics. So there's no biological reason to think that we wouldn't have the same treatment effect in black patients or any other specific race, for that matter. And very importantly, there are no safety concerns in this population. So in totality, we feel that the data support the use across all races and demographic groups.

With regard to women, the comments are largely the same. This is a very small subgroup, which is representative -- which is reflecting the

known demographics of the disease. This is well recognized to be a male predominant disease and, again, that means that while we're reflecting the demographics, we're left with a very small subgroup with wide confidence intervals. And again, this has been tested statistically, and there is no significant difference in the results between these subgroups.

DR. WILDER SMITH: So that's really helpful information. I guess my only other comment -- well, one comment is just to say that you also have a small sample of Asian participants, and you do have wide confidence intervals but you're not seeing necessarily the same trends in the means.

Have you looked at any of these outcomes prior to the deaths? Even at months earlier, you had longitudinal data -- I think it's 6 months and 9 months -- and I'm curious if you looked at any of the subgroup data earlier.

DR. VEST: We don't have those analyses. You had also asked part of your question about

whether or not we've done subgroup analyses during the open-label extension, and we do not have those analyses at this time.

DR. WILDER SMITH: Thank you. That's all I have.

DR. BUTLER: Thank you, Dr. Smith.

We are running a little bit behind, so we'll take one last question from Ms. Abernathy, and I will request, Dr. Thadhani, that we will find some opportunity later in the meeting for more clarifying questions.

Ms. Abernathy?

MS. ABERNATHY: Thank you. I realized that the population, especially for the genetic version of amyloidosis was quite small, but was there any consideration in the study to assure that there was a mix of variant types?

MR. SLUGG: Sure. Let me have my colleague, Dr. Vest, address your question.

DR. VEST: John Vest, Alnylam. We sought, in enrolling the study, to accurately and comprehensively reflect a global population, and we

feel that we achieved that with regard to the hereditary and wild type. We have about 20 percent hereditary, which is reflective of the demographics of the disease. I think you're also asking about the difference in mutations. We do have 16 mutations represented on APOLLO-B. The most common is the V122I mutation, which is about 40 percent, followed by T60Ala, about 18 percent, and that's, again, reflecting the nature of the disease.

We're showing here the forest plots; that we do have consistent results in both hereditary and wild-type disease. And then importantly, we also see entirely comparable TTR reduction, and that's also a property that's well understood with this drug, which targets a common region of the gene and is equally effective in suppressing both wild type and all known mutations of this disease.

MS. ABERNATHY: Thank you.

DR. BUTLER: Thank you, Ms. Abernathy.

This now concludes this session. We will now take a quick 10-minute break. Panel members,

please remember that there should be no chatting or discussions of the meeting topics with other panel members during the break. Since we are running a little behind, let's please make sure that we are back and resume the meeting at 11:18 am.

(Whereupon, at 11:08 a.m., a recess was taken, and meeting resumed at 11:18 a.m.)

DR. BUTLER: It is 11:18, so let's continue with the meeting. We will now proceed with the FDA presentation, starting with Dr. Rosalyn Adigun.

FDA Presentation - Rosalyn Adigun

DR. ADIGUN: Thank you, Dr. Butler.

Good morning. My name is Rosalyn Adigun, and I'm a clinical reviewer in the Division of Cardiology and Nephrology, FDA, CDER. I will be presenting a summary of FDA's review of the efficacy assessment and evaluation of the clinical meaningfulness of patisiran in the treatment of transthyretin amyloid cardiomyopathy.

I will start with topics that we would like the advisory committee to opine on during the course of today's meeting. First, is the extent of

the observed effect of patisiran clinically relevant? And second, does patisiran have benefits in patients with transthyretin amyloid cardiomyopathy who are also taking standard-of-care tafamidis?

A quick recap of the APOLLO-B study, APOLLO-B was a phase 3 trial that provides evidence of safety and efficacy for patisiran use in the treatment of transthyretin amyloid cardiomyopathy. This was a 12-month, randomized, double-blind, placebo-controlled trial. The study enrolled adults with transthyretin amyloid cardiomyopathy and stratified randomization by baseline tafamidis use, genotype, New York Heart Association functional class, and age.

The primary endpoint was change from baseline at month 12 in the 6-minute walk test. The first key secondary endpoint was change from baseline at month 12 in the Kansas City Cardiomyopathy Questionnaire Overall Summary Score. The other secondary endpoints include a composite of all-cause mortality; frequency of cardiovascular

events; and change from baseline in the 6-minute walk test; a composite of all-cause mortality; frequency of all-cause hospitalizations and urgent heart failure visits in patients not on tafamidis at baseline; and a composite of all-cause mortality; frequency of all-cause hospitalization; and urgent heart failure visits.

Based on our review of the APOLLO-B trial, we can conclude the following observations. APOLLO-B was a well-conducted phase 3 trial. Discontinuation of study drug was balanced between patisiran and placebo groups. There was less than 10 percent missing data in each arm. The safety results of APOLLO-B was largely consistent with the safety data from the hereditary transthyretin-mediated amyloidosis polyneuropathy population and with the expected risk for patients with ATTR cardiomyopathy.

Additionally, APOLLO-B met two of its prespecified efficacy endpoints, the primary endpoint, change from baseline at month 12 in the 6-minute walk test, and the first secondary

endpoint, change from baseline at month 12 in the KCCQ Overall Summary Score. The next bullet here is the main reason we're here today; however, there was a small treatment effect in patients treated with patisiran compared with placebo.

For the primary endpoint, there was a median difference of 6-minute walk test of 14.7 meters at month 12; this in a cohort of patients with a median baseline performance on the 6-minute walk test of 364 meters. For the first secondary endpoint, there was a mean difference in the KCCQ Overall Summary Score of 3.7 points; this also in a cohort with a mean baseline KCCQ Overall Summary Score of 70 out of 100.

Before we proceed further with specific information related to the efficacy of patisiran in APOLLO-B or the clinical meaningfulness of the treatment effects observed, I would like to take a few minutes to discuss the general framework of endpoints used to establish effectiveness in clinical trials.

Evidence of effectiveness in a clinical

trial can be based on clinical hard endpoints. Examples of this would be myocardial infarction or stroke. Surrogate endpoints, an example would be blood pressure, or specific to APOLLO-B, clinical endpoints that reflect how patients feel or function. When the clinical benefit of a drug is established based on how patients feel or function, this approach uses patient-centric clinical outcome measures to derive these endpoints. If a patient cannot detect a treatment effect or cannot appreciate the treatment having an impact on their health, then the treatment effect is not clinically meaningful to the patient.

FDA guidance provides examples of acceptable COA-based endpoints. 6-minute walk test is an example of an acceptable functional measure for ATTR cardiomyopathy. KCCQ is an example of a measure for ATTR cardiomyopathy that can generate acceptable COA-based endpoints. To establish clinical benefit, a drug must be shown to have an effect in an adequate and well-controlled trial that is both statistically persuasive and

clinically meaningful.

Prior to the initiation of APOLLO-B, FDA and the applicant were aligned on the endpoints appropriate for a cardiomyopathy claim. Guidance provided stated that the proposed study should demonstrate a meaningful improvement in a clinical outcome such as cardiovascular death and hospitalization for heart failure. Alternatively, meaningful improvements in functional testing or health-related quality-of-life measures could suffice if a predetermined level of harm with respect to death and hospitalization could be excluded.

A few months before the first patient was enrolled in APOLLO-B, first-in-class therapy for treatment of ATTR cardiomyopathy was approved. The implication of this approval on the clinical trial design was addressed. FDA did not object to the sponsor's proposal to limit the number of patients on background tafamidis based on the rationale that access to the newly approved therapy would vary by region.

Over the next few slides, we will look at the effects of patisiran in APOLLO-B and if the observed effects are clinically relevant. A quick reminder of the key features of patients studied in APOLLO-B; this was a predominantly older male population, white, with cardiomyopathy of wild-type TTR. Most of the patients had stage 1 disease and NYHA functional class II symptoms. Baseline demographics were similar between patisiran and the placebo arms.

For the primary efficacy endpoint, change from baseline at month 12 in the 6-minute walk test, both patisiran and placebo-treated patients showed declines. Using the applicant's prespecified analysis method, patisiran demonstrated a statistically significant smaller decline in 6-minute walk test at month 12 compared to placebo. The Hodges-Lehmann estimate of median difference was 14.7 meters with a 95 percent confidence interval between a 0.7 to 28.7 meters.

The empiric cumulative distribution function, or ECDF curves, displays a continuous

view of change, both positive and negative, from baseline at month 12 in 6-minute walk test distance. This is shown on the horizontal axis. On the vertical axis, the cumulative proportion of patients with a particular level of change or higher is represented. The ECDF curves allow a variety of change scores to be examined, both simultaneously and collectively in composite all available data.

Despite achievement of statistical significance, the change from baseline at month 12 in 6-minute walk test was small, and this is evident by the minimal separation between the treatment arms. Placebo is depicted in red and patisiran in blue. For 6-minute walk test, a negative change -- that is a change less than 0, which is to the left of the centered vertical line -- represents worsening. This is particularly important, as both arms showed decline in 6-minute walk test, and the objective of the study was to slow the progression of disease.

For the first secondary endpoint, that is

change from baseline, in KCCQ Overall Summary Score, the primary analysis was based on a mixed model for repeated measures or MMRM. Based on this analysis, patisiran demonstrated a statistically significant change from baseline of 3.7 points and a 95 percent confidence interval between 0.2 to 7.2 points.

Taking a look at the ECDF curve for the first secondary endpoint change from baseline at month 12 in the KCCQ Overall Summary Score, the least square mean difference was 3.7 points on a 0-to-100 transformed scale score. This change was considered small. This is also evident by the minimal separation observed between the treatment arms. For KCCQ Overall Summary Score, a positive change, that is a change greater than 0, can be seen to the right of the vertical centered line, and that represents an improvement.

Now, looking at the trajectory of patisiran's treatment effect on 6-minute walk test to the left and the KCCQ Overall Summary Score to the right, over the double-blind period, we see

that for 6-minute walk test, patisiran and the placebo curves showed similar declines for the first 6 months. Looking to the end of the double-blind period, there appears to be no divergence of both treatment arms. For the first secondary endpoint, change from baseline at 12 months in the KCCQ Overall Summary Score, the mean difference between the arms was 3.7 points; this on a transformed scale of 0 to 100. The scale used for the vertical axis showing the mean change from baseline amplifies a small area of the data and does not adequately represent the magnitude of treatment effect, which was small in this endpoint.

A few comments about the other secondary endpoints, for the first composite endpoints of all-cause mortality, frequency of cardiovascular events and change from baseline in 6-minute walk test, a stratified win ratio test was used. The hierarchical composite is driven here by the 6-minute walk test component. This was modeled as a continuous measurement. As a result, even a 1-meter change can determine a winner or a loser.

These results should be interpreted with caution. None of the other secondary endpoints showed a statistically significant treatment effect.

To summarize the efficacy findings of APOLLO-B, the treatment effects for 6-minute walk test and KCCQ Overall Summary Score were statistically significant, but small. For the primary endpoint, there was a median difference of 14.7 meters; this in a cohort of patients with a median baseline performance of 364 meters. Sensitivity analyses and additional supplementary analyses performed on the primary endpoint yielded smaller estimates. For the first secondary endpoint, there was a mean difference of 3.7 points on the KCCQ Overall Summary Score. Sensitivity analyses yielded consistent treatment effects.

APOLLO-B did not show a treatment effect on any of the other secondary endpoints. The trial also did not show a benefit on mortality or irreversible morbidity. Efficacy results from the open-label extension phase up to month 24 are uninterpretable. Remember, all subjects were now

receiving patisiran. There is also potential for bias in our interpretation of efficacy endpoints due to knowledge of the treatment assignments.

So how small were the effects of patisiran observed in APOLLO-B? To visually describe these results, we represent the treatment effects of patisiran on the 6-minute walk test and the KCCQ Overall Summary Score in the tables shown. On the left is a visual depiction of the 6-minute walk test results, and on the right, the KCCQ Overall Summary Score. Baseline performances are shown in blue and the month 12 performances in red. It is reasonable to conclude that the difference between both groups shown are difficult to perceive and not unreasonable to wonder if these could be detected or perceived by patients.

One of the key considerations in regulatory decision making is the evaluation of how well the results of a COA-based endpoint corresponds to a treatment benefit that is meaningful to patients. The agency has been consistent in communications, from the 2009 patient-reported outcome guidance to

the recently published patient-focused drug development guidance series, that an anchor-based approach is a useful method for understanding what the patient would regard as clinically meaningful; that is, what constitutes an improvement or deterioration from a patient's perspective?

An anchor is an external variable -- not derived from the COA whose scores require interpretation -- for which meaningful differences are directly interpretable or already known. The interpretation of an anchor-based analysis depends on the appropriateness of the selected anchor variable, and our guidances provide several considerations on the choice of suitable anchor variables.

Other methods, such as qualitative exit interviews or surveys, can also be used in addition to or instead of an anchor, especially when an anchor-based method or an appropriate anchor does not exist; however, approaches such as distribution-based methods using an effect size or a standard deviation, or model-based approaches,

are inappropriate as a primary method to determine what is clinically meaningful, as they do not directly take into account the patient's perspective.

Now, applying the FDA guidance to the results observed in APOLLO-B, there were neither appropriate anchor skills administered, nor qualitative data collected, to aid in the evaluation of the clinical meaningfulness of the treatment effects of 6-minute walk test or KCCQ Overall Summary Score from the perspective of patients. As a result, there was no evidence provided to show that the treatment effects on 6-minute walk test or the KCCQ Overall Summary Score are clinically meaningful to patients.

Additionally, the applicant's analyses didn't align with FDA guidance. For 6-minute walk test, the sponsor used KCCQ Overall Summary Score, the key secondary endpoint, and KCCQ physical limitation score as anchors. Both of these scores require interpretation of their own. For the secondary endpoint, the sponsor referenced other

heart failure products for which a claim for symptomatic improvement was not granted by the agency.

I will now transition to the second topic relevant to the discussion today. Does patisiran have benefits in patients with transthyretin amyloid cardiomyopathy who are already taking standard-of-care tafamidis?

The treatment landscape for transthyretin amyloidosis is evolving; however, tafamidis is currently the only FDA-approved therapy indicated for the treatment of transthyretin amyloid cardiomyopathy. Evidence of safety and efficacy for tafamidis is based on the results of the ATTR-ACT trial, a 30-month, multicenter, double-blind, placebo-controlled study in patients with transthyretin amyloid cardiomyopathy randomized to tafamidis or placebo.

The primary endpoint was a hierarchical composite of all-cause mortality and frequency of CV-related hospitalizations at month 30. The secondary endpoint was change from baseline at

month 30 in 6-minute walk test and KCCQ Overall Summary Score. Based on the findings of the ATTR-ACT trial, current guidelines recommend the use of tafamidis in patients with ATTR cardiomyopathy and NYHA functional class I, II, III heart failure symptoms to reduce cardiovascular morbidity and mortality.

While the primary efficacy endpoints for tafamidis were clinical endpoints, the study also assessed the effects of tafamidis on symptom and function endpoints that reflect how patients feel and function. For the current standard of care, tafamidis, there was a mean change of 33 meters at 12 months in the 6-minute walk test and a mean change of 8 points at 12 months in the Kansas City Cardiomyopathy Overall Summary Score, with continued separation of the treatment groups through the end of the double-blind period.

Before we discuss the results of the tafamidis subgroup in APOLLO-B, it is worth mentioning that tafamidis is now the standard of care in patients with transthyretin amyloid

cardiomyopathy, and in the patisiran expanded access program, 96 percent of patients are also receiving tafamidis. So what did we observe when we looked at the tafamidis subgroup in APOLLO-B? Ninety-one of the 359 patients, 25 percent of the cohort, were on background tafamidis.

Patients on background tafamidis showed neutral results. For the primary endpoint, change from baseline at month 12 in the 6-minute walk test, patients treated with patisiran compared with placebo on a background of tafamidis demonstrated a median difference of negative 4.2 meters, where negative numbers favor placebo, with a wide 95 percent confidence interval between negative 29 and 20.5 meters. And for the KCCQ Overall Summary Score, patients treated with patisiran compared with placebo on a background tafamidis demonstrated a mean difference of 2.1 points, with a 95 percent confidence interval between 5 and 9 points.

Consistent with the agency's view on subgroup analysis in clinical trials, subgroup analyses are viewed as exploratory. They're

hypothesis generating, exploring the effects of an intervention across the range of baseline factors, and we always are cautious about the risk of an inflated type 1 error with no multiplicity control. With regards to the patisiran plus tafamidis subgroup in APOLLO-B, there is biological plausibility for additive effects when patisiran is used with tafamidis, as both therapeutics target different steps in the disease pathway, but neither addresses the effects of preexisting end-organ involvement.

There was a small number of patients, 25 percent of the randomized cohort, and the wide confidence interval increases uncertainty. It is also important to note that APOLLO-B was not designed nor powered to provide definitive conclusions regarding the efficacy of patisiran in patients on tafamidis.

I will conclude the presentation with the following remarks. We observe a small treatment effect of patisiran on 6-minute walk test and the KCCQ Overall Summary Score; however, there is no

evidence that these small treatment effects are meaningful to patients. All-cause mortality and cardiovascular events over the double-blind period were not significantly improved; however, we recognize that this study was not powered for mortality endpoints. And finally, it remains unclear what to do in patients on background therapy with tafamidis. I will now conclude the FDA portion of the presentation. Thank you.

Clarifying Question to FDA

DR. BUTLER: Thank you very much, Dr. Adigun.

We will now take clarifying questions for the FDA presenter. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number if possible.

Finally, it will be helpful to acknowledge the end of your question with a thank you and end of your follow-up questions with, "That is all for my questions," so that we can move on to the next panel member.

I will now request Dr. Noel Bairey Merz to ask her question.

DR. BAIREY MERZ: Thank you, Dr. Butler. I have a question. It's slides 18 and 19, but I think we can just take it verbally again, and it's similar to an earlier question.

There actually are anchors to the KCCQ, as well as other metrics -- angina scores -- that a change of 5 is considered a small but clinically meaningful effect. It sounds like it was not discussed in advance with the FDA. This is a similar question that we posed to the sponsor. Thank you.

DR. SENATORE: My name is Fred Senatore. I'm lead physician, and I've been privileged to triage the questions, so for this question, I will call on Dr. Morell from our PFFS group to respond.

DR. MORELL: Thank you. I'm Dr. Monica Morell, psychometrician and statistical reviewer on Patient-Focused Statistical Scientist group in CDER. We acknowledge that much of the literature on KCCQ suggests that a small clinical difference in scores is 5 points. FDA CDER has concerns with the 5-point change threshold as clinically meaningful from the patient's perspective.

We note that the 5-point change was derived in a single study, which itself had limitations such as the anchor scale used and the prioritization of the clinician perspective above patient voice. Considerations for clinical management, clinical research, and regulatory decision making are not necessarily the same. We need to make evidence-based decisions that are supported by the trial data provided for our review. Thank you.

DR. BAIREY MERZ: Dr. Butler, I have a follow-up question.

DR. BUTLER: Please.

DR. BAIREY MERZ: So therefore, something

less than 5 might be considered meaningful since there's no acknowledged metric that the FDA considers would be clinically meaningful currently today?

DR. MORELL: Thank you for the question. At the moment, we have no evidence on what might be a clinically meaningful change on the KCCQ.

DR. BAIREY MERZ: Thank you. That's satisfactory, Dr. Butler.

DR. BUTLER: Thank you very much, Dr. Bairey Merz.

May I request Dr. Chris O'Connor to ask his question?

DR. O'CONNOR: Yes. Chris O'Connor for the FDA team, maybe the statistical team. I'm curious of the opinion of the FDA on the statistical interaction with a p-value of 0.06 with patients prior treated with tafamidis or not. Do you believe that's a meaningful interaction? And given that the primary and top secondary results appear stronger in those in the non-tafamidis group, do you think that's meaningful?

DR. SENATORE: Thank you, Dr. O'Connor. I will call on Dr. Zheng to provide a response.

DR. ZHENG: Hi. This is Mengjie Zheng. I'm the statistical reviewer. First of all, the study is not powered to test the interactions, so the p-value, we don't have a lot of confidence being able to distinguish there is a difference between the two subgroups. Also, this interaction will not answer the question whether there is effectiveness in the tafamidis subgroup or not. Thank you.

DR. O'CONNOR: Let me just clarify, Dr. Butler, if I may.

Really, the the question I have is whether the non-tafamidis group you feel is meaningful, many people believe that when you prespecify a subgroup to test an interaction and you obtain a p-value of 0.06, were never powered in subgroups adequately, but that suggests a pretty strong relationship, as the sponsor mentioned. Usually 0.1 is what we start to consider of interest if a p-value is less than 0.1 in a test for interaction of a subgroup. Again, how do you feel about the

information in the non-tafamidis group as far as the efficacy endpoints?

DR. SENATORE: I'll call upon Dr. Jialu to provide a response.

DR. ZHANG: I'm Jialu Zhang, the statistician, FDA. As Dr. Zheng stated, this interaction, the study is not powered to test any interaction. It also doesn't address whether a particular subgroup -- it's not powered to address if a particular subgroup is effective or not. We can only look at it to see whether there's a consistent trend, but it's not designed to answer whether on top of tafamidis it's effective, or not on tafamidis it's more effective.

DR. BUTLER: Any follow-up questions, Dr. O'Connor?

DR. O'CONNOR: No, but I don't agree with that response.

DR. BUTLER: Thank you. Thank you for your perspective.

Dr. Thadhani?

DR. THADHANI: Thank you, Dr. Butler. I

have two questions. I was impressed by the distribution function figures, and if the agency can refer to those figures for the following question; that is, is the interpretation of those distribution functions that the majority of patients actually did not benefit?

Yes, the differences reach p-values that were significant and they were small, but based on those distribution function figures, should we interpret the results as majority, meaning over 50 percent, did actually not respond to either of those measures or were not responsive on either of those measures?

DR. SENATORE: Thank you. I will call upon Dr. Zhang to respond or to invite her to ask someone else to chime in.

(Pause.)

DR. SENATORE: We've had some technical difficulty. Could you kindly repeat the question, please?

DR. THADHANI: Sure; happy to. If the agency can refer to the distribution function

figures and just help us interpret them. Was the agency meaning to imply that the majority of patients did not actually respond to either 6-minute walk test benefit or the KCCQ? Again, based on those figures, it seemed as if almost 60 percent were non-responsive or did not improve on either measure.

DR. SENATORE: I will ask Dr. Garrard to come up and respond.

DR. GARRARD: Hi. This is Dr. Lili Garrard. I'm a statistician. Your interpretation is correct. If you look at ECDF curves, if you look specifically at the vertical line at zero, we can see that the majority of patients on either arm did not experience a change. Thank you.

DR. THADHANI: Thank you, Dr. Butler. Could I have one additional question?

DR. BUTLER: Yes, please.

DR. THADHANI: The agency made a comment that while the functional measures, which have been used in other clinical trials, have been used perhaps as supportive measures to demonstrate

benefit of an agent or an intervention, that, in fact, approvals, registration approvals, were not based on those functional measures.

Has there historically been from the agency any trials, the primary measures being functional, where there has been an approval based solely on those functional measures, and if so, at what thresholds?

DR. SENATORE: I will ask Dr. Pretko to come up and respond.

DR. PRETKO: Hi. I'm Susan Pretko, reviewer for the Division of Clinical Outcome Assessments. There have been approvals where functional measures were used as primary endpoints; however, they have been in other indications or other therapeutic areas, so the results could not necessarily be extrapolated to this program. Thank you.

DR. THADHANI: Thank you. But is it clear or is it the case that the studies that were shown by way of a figure -- I don't remember what number the figure was -- that for those primary studies, they were not approved, based on those functional

measures?

(Pause.)

DR. SENATORE: Dr. Thadhani, was that a follow-up question you were asking?

DR. THADHANI: Yes. I was just clarifying, the figure that was shown -- apologies. I should have stated this. The figure that was shown in terms of the studies demonstrating even small effect sizes on functional measures, for the most part, agents were not approved from those studies based on the functional measures shown thus far. I just wanted to clarify that with the agency again.

DR. SENATORE: Dr. Stockbridge will respond

DR. STOCKBRIDGE: Yes. The sponsor showed a plot from a number of different drugs and the magnitude of treatment effect that was there, but the majority of those don't have a claim based on those results.

Does that address your question?

DR. THADHANI: Yes, sir. Thank you.

That's all I have, Dr. Butler. Thank you.

DR. BUTLER: Thank you, Dr. Thadhani.

May I request Dr. Soergel to ask his question?

DR. SOERGEL: Thank you, Dr. Butler. David Soergel. I am the industry representative. Related to Dr. Thadhani's question, I found the analysis looking at KCCQ and its relationship to 6-minute walk duration as being pretty intriguing, especially in this older patient population in a relatively rare disease.

I have two specific questions, the first to the agency. What about the KCCQ, in particular, does not meet the criteria for an anchor measure? And then the second question related to that is, if we can include KCCQ as an endpoint in our clinical trials, it seems to me that there should be some relationship between including that endpoint in the study and its clinical meaningfulness. This protocol was discussed with the agency ahead of time, so I'm curious about the dialogue about KCCQ and the thresholds of meaningfulness that were discussed during those initial interactions. Thank you very much.

DR. SENATORE: Thank you. I will call on Dr. Morell to respond to this question.

My apologies. I will call upon Dr. Pretko to respond to this question.

DR. PRETKO: Thank you for that question. Will you please bring up slide 67? I'll go ahead and start speaking to this.

The KCCQ Overall Summary Score was proposed to be used as an anchor scale. There are 20 items that contribute to that OS score, and actually only six of them assess physical function. We agree that those physical function items, they may be related to aspects of physical functioning, but we note that some of those items, there's an item assessing dressing yourself and there's an item assessing showering, so those may not be closely related to the distance a person can walk in 6 minutes.

Then there are other items that contribute to the quality of life and social limitations domain, and those items assess concepts such as feeling discouraged, missing family or friends, out

of your house, and intimate relationships with loved ones. And these concepts, again, they're more distal, so they may not be related to functional capacity and may be imposed by factors unrelated to the treatment or disease, which contributes to a part of the limitations, so that this has an anchor scale. Thank you.

DR. BUTLER: Dr. Soergel, do you have any follow-up clarification?

DR. SOERGEL: Yes, just one clarification around the use of KCCQ as an endpoint. For example -- I think Dr. Bairey Merz mentioned this in her question as well -- the change of 5 points is generally recognized, as was shown in the sponsor's presentation, as being a meaningful change, either in a positive direction or a negative direction. So it seems to me that this interaction between KCCQ and 6-minute walk, again, it sounds relatively persuasive from the sponsor's side. So I'm trying to understand, in this older population in a rare disease, where you're not going to have the benefit of having a lot of data

to anchor on, is this an adequate way of looking at clinical meaningfulness in this study?

DR. SENATORE: I will call upon Dr. Pretko again, please.

DR. PRETKO: I'm sorry. Please repeat the question.

DR. SOERGEL: Yes. To repeat, I'm interested that this is a rare disease in an older population where we don't have a lot of data to anchor, so the sponsor is hypothesizing that clinical meaningfulness in 6-minute walk duration, the distance is going to be shorter in this population. And they showed, I think, a relatively persuasive analysis looking at generally accepted changes, negative and positive changes, on KCCQ and correlating those. So I'm just curious on your reaction to that and how we should interpret that analysis.

DR. PRETKO: Thank you so much. So in the setting of this program, we need alternative evidence to demonstrate that amount of change is going to be meaningful in this older population;

however, we do not have that evidence available to us.

DR. SOERGEL: Thank you, Butler.

DR. BUTLER: Thank you, Dr. Soergel.

May I call upon Dr. Roy-Chaudhury to ask his question?

DR. ROY-CHAUDHURY: Yes. Thanks to everyone. My question was really about the change in, let's say, the 6-minute walk test relative to the baseline, and I was trying to work out whether some of this information could come from the distribution curves, and I felt not. The question really was, was the distribution the same across the different baseline levels? I'm coming from the setting where a change of 6 in somebody who had a baseline 6-minute walk test of 200 actually would mean a lot more than, let's say, a change of 8 in somebody who started off at a baseline of 400.

Is there any information on this? I'm coming from this, really again, just from a patient perspective and understanding also about the durability of the effect, which was potentially

discussed earlier.

DR. SENATORE: Thank you. I'll call upon Dr. Stockbridge to come here, please.

DR. STOCKBRIDGE: Could you maybe put up the cumulative distribution plot for 6-minute walk? That's slide 11. Our interpretation of this is that there's no evidence of a part of that distribution, which is different for the two groups; that is, if you were on the left-hand part of it, you got about the same benefit as if you were in the right-hand part of that distribution. That doesn't quite go to the issue you raised about the baseline, but it doesn't suggest that there's a difference with some patients getting a substantially larger benefit than others.

DR. ROY-CHAUDHURY: Thanks, Dr. Stockbridge, and that will be all for me at this point, Dr. Butler.

DR. BUTLER: Thank you, Dr. Roy-Chaudhury.

May I ask Dr. Kasper to ask his question?

DR. KASPER: Thank you, Dr. Butler. In regards to this particular issue of anchoring, does

the FDA have an idea of what would have been a better way to have done this, other than the KCCQ? What else out there could they have anchored on? And that would be my only question. Thank you.

DR. SENATORE: Let me call upon Dr. Pretko to respond to this.

DR. PRETKO: Thank you for your question. So an ideal anchor scale to interpret change in 6-minute walk test might ask about the patient's perception of their walking ability or how far they're able to walk. Our guidance does recommend using multiple anchor scales to triangulate and interpret [indiscernible] based endpoints, an additional anchor scale or more than one anchor scale. Also, including an anchor scale assessing physical function would also have been helpful to interpret 6-minute walk test change scores. Thank you.

DR. BUTLER: Thank you very much.

May I request Dr. Cella to ask his question?

DR. CELLA: Thank you. Dr. Butler. This is kind of a follow-up to what Dr. Thadhani was

getting at and relates to precedence with these two endpoints.

I recognize that we have different therapeutic areas, but since both of these endpoints, 6-minute walk and the KCCQ Overall Score, have found their way into previous labels, could you give us something like a range of group differences that existed in those labels? I realize that may be a hard question because someone would have to know all these numbers, but it would be helpful to know, in terms of precedence, what kinds of magnitude has made it into labels for these endpoints, regardless of clinical area.

DR. SENATORE: I'll start off by asking Dr. Pretko to comment, and she could refer other people to comment afterwards.

(Pause.)

DR. CELLA: That's my only question, Dr. Butler, so I'll go off screen.

DR. BUTLER: Thank you.

DR. PRETKO: Thank you. Sorry for the delay. I'm having technical trouble.

DR. BUTLER: But we could hear you.

DR. PRETKO: Okay. I'll -- [inaudible].

DR. STOCKBRIDGE: Well, I don't think we're going to have a satisfactory answer for that. I don't think anybody's gone through and tried to catalog where we've agreed or not. I can, however, point out that this study was powered for a treatment effect on 6-minute walk that was twice as large as what was observed, and the upper confidence limit essentially rules out an effect as large as what was proposed.

So with that all in mind and with the APOLLO results, which showed substantial improvements in symptomatic effects, there was no real anticipation on anybody's part that we'd be discussing what was minimally clinically relevant here. The expectation was you'd see something similar to what you saw in the APOLLO study, and the effects would have been large enough not to have raised this concern.

DR. BUTLER: Thank you. Thank you, Dr. Stockbridge.

So we have gained a little bit of time in this session. There were some questions to the applicant for clarification that we could not get to because we were running out of time in the previous session, so I would request if anybody has questions for the applicant to come back as well.

I actually have a question for the FDA, but before I ask my question, I saw Dr. Kovesdy's hand up, and then it's down. I'm going to assume that his question was asked by someone else, but if that's not the case, and if this was a technical glitch, please raise your hand again.

My question to the FDA is that I'm still trying to get my head around the rationale of why there was a cap for tafamidis at 25 percent. The rationale that it's a new therapy, we don't know what the global uptick might be, and all of those are genuine comments, but I would think that that would lead to the opposite conclusion that you want a minimum number of 20, 25, whatever it is, to get a sense of benefit on and off tafamidis as opposed to imposing a cap rather than a minimum number. So

that's my first question.

The second question is that this will be highly exploratory. I don't know how to interpret that, but still, has the FDA done any secondary analysis that if we look at the differences in those with and without tafamidis, what proportion of patients -- if they were on tafamidis in this study -- in that study might not have reached the primary endpoint?

DR. SENATORE: Thank you, Dr. Thadhani [sic]. I'll call Dr. Stockbridge to respond.

DR. STOCKBRIDGE: Yes. So we didn't set a cap on tafamidis use. The sponsor set a cap on tafamidis use, and we thought it was not unreasonable. I think there was reasonable concern that perhaps this wouldn't -- as you might expect from the mechanism, this might not add to tafamidis. So driving down the event rates and with the symptom improvement that you got with tafamidis, it would be hard to show a treatment effect.

So I think the restriction that the sponsor did was reasonable and still gave us some opportunity to see whether or not the effects in the patients on tafamidis trended favorably, and depending on where you look, they either did or didn't. But that's where we got it. It was not us setting a cap.

DR. BUTLER: Great. Thank you, Dr. Stockbridge.

We will open the rest of the session both for clarifying questions to the FDA or the applicant. And also I would like to give the opportunity to the applicant, that there were three questions for which they were going to look at the data during the break and come back after lunch. But just in case, if they have located those data and they want to take the opportunity at this time to present those, we can accept that as well.

But let me now move on to Dr. Roy-Chaudhury for his question.

DR. ROY-CHAUDHURY: Yes. Thanks, Dr. Butler. This is a question to the FDA group.

I guess it's maybe a little bit of a philosophical question, but could the FDA comment on what they think about the durability of the effect in the treated group versus what seems to be an inexorable decline in the non-treated group as it comes out from the open label study, and whether that is of importance, particularly when you're thinking from the patient perspective? If you say that 14 meters becomes 28 and then becomes 42 over a period of time, it could be quite important to patients.

DR. SENATORE: To clarify your question, are you asking about the open-label extension and the possible effect?

DR. ROY-CHAUDHURY: Yes, I am, and whether that factors in, in any way. And the answer may well be we're just looking at the primary endpoint.

DR. SENATORE: If I could call upon Dr. Adigun to come up here and respond to your question.

DR. ADIGUN: Thank you for that question. Dr. Adigun here, clinical reviewer, DCN. I do appreciate the question. The challenge now in the

open-label extension phase is we have to remember that more patients are now on tafamidis, and it becomes difficult because now there is potential for bias as we're looking at this patient population, so to be able to make a conclusion at this point in the open-label extension phase becomes more difficult. I do understand the fact that you do see some durability of effect, but there are other also potential confounders that could influence what we're seeing in the open-label extension phase.

DR. ROY-CHAUDHURY: That's actually, I think, very important information for me. Just as a follow-up, then, do we have an idea of the tafamidis penetration, if you will, in the open-label phase?

DR. ADIGUN: Maybe the applicant can give us a better idea of how many patients are now on tafamidis since the open-label extension phase started.

MR. SLUGG: Yes. Thanks very much, Dr. Adigun. This is Andrew Slugg from Alnylam. We

do have those data regarding the patients who dropped in on tafamidis during both the double-blind and placebo-controlled period, and we show those data here. Sorry. I had to transfer back over to us, and we'll share them with you.

The number of patients, as you can see here, is depicted. The first row is the number of patients who have dropped in on tafamidis during the placebo-controlled period, and the second row is either the placebo-controlled or open-label period, relatively low, only six on patisiran during the entire 24 month period and only 10 on placebo. Of course, half of that treatment period is patients rolling over onto patisiran after treatment.

DR. BUTLER: Thank you.

MR. SLUGG: We can also address some of the agency's prior comments. We don't have all of the information available, but there was a question I think from Dr. Cella regarding the number of patients -- forgive me if that's wrong -- and the different threshold analyses we performed, the

KCCQ. So we do have that information here, and we can have that presented, at least orally, while we prepare a slide for you that would help the committee.

DR. BUTLER: Certainly. Please go ahead.

MR. SLUGG: Sure. We have these data. We can have Dr. Spertus kind of walk you through these data and now present them to you.

DR. SPERTUS: Thank you very much. Dr. Cella asked for the number of patients in the different groups and what the distribution looked like. Is it possible to share this with you? We will be sharing this with you later, but we actually do have the number of patients across the different categories, and we also have it divided in increments of 5 to 10 and greater than 10, so that we can provide the greater granularity requested.

In summary, since you can't see the data directly, there's a very comparable relationship, is what we showed, looking at 5 points or lower, with about 42 patients in patisiran and 33 patients

in placebo, representing 24 percent and 19 percent of the population, increasing by greater than 10 points -- increasing by greater than 5 points mirrors what we showed you before. Decreasing by 5 points, or dying, was reflected in 64 of the patients treated with patisiran and 76 percent of the patients treated with placebo; and then declining by 10 points or greater, or dying, was in 45 patients in patisiran and 56 patients in placebo, representing 25 percent and 32 percent of the population.

I also wanted to address Dr. Morell's comment about whether a 5-point difference was clinically meaningful or not. In the article, we argued -- and this is a 2005 publication in the American Heart Journal describing what's a clinically important difference, and we did emphasize using the clinician's assessment of change, with the argument that the patient's voice was captured in the KCCQ itself, and that the physician, having seen many, many patients over time, would have a more reproducible assessment.

We did, however, publish the data across all of the scales, describing from the patient's perspective and the physician's perspective what a clinically important change is, and from the patient's perspective, a small but clinically important improvement or deterioration tends to be smaller than that of the clinician. So the mean change in the KCCQ of patients who reported that they themselves had a small but clinically important improvement was only 1 point, and a deterioration was only 2.9 points. And I'd be happy to provide the FDA that article, which was in the Journal of Quality of Life. Thank you very much.

DR. BUTLER: Thank you, Dr. Spertus.

May I request Dr. O'Connor to ask his question?

DR. O'CONNOR: Yes. Could the sponsor pull up slide 8? I'm still confused by my COVID question. The clinical trials that we participated in, many heart failure trials, we went into lockdown in March of 2020 for about a year, and we

converted our 6-minute walk assessments and KCCQ assessments to home-based or tele-based methods. It looks like the majority of your enrollment occurred when the U.S. was locked down. Was there no interruption in the assessment of your endpoints because of the COVID pandemic? I think that's how you responded to my question.

MR. SLUGG: Yes, Dr. O'Connor. Your understanding is correct. There was no impact on the assessments due to COVID. We did take measures to ensure, especially for this rare disease, we're able to get patients into the clinic using the validated course, along with using the validated instructions that were established at the beginning of the trial.

DR. O'CONNOR: Okay. I'm impressed how you were able to limit the drop-in of tafamidis post-randomization, given that it was approved and it was a guideline, 1A recommendation with such strong clinical implications. How did you do that?

MR. SLUGG: The drop-in was not at all limited by the sponsor. In fact, every informed

consent the patients signed in this trial were informed that there was an approved therapy that was shown to be safe and effective and was approved for the slowing of congestive heart failure and that they had a mortality benefit. So these patients were informed of the availability of tafamidis. If it was available in their territory, it was part of the informed consent process, and they were consulted as part of the entry into the study. So all patients were made very much aware of the availability of tafamidis, yet still decided to participate in this trial.

DR. BUTLER: Thank you, Dr. O'Connor.

May I request Dr. Thadhani to ask his question?

DR. THADHANI: Thank you, Dr. Butler. This is a question for the sponsor. It's two questions in particular, and that is the validity of TTR levels as a potential surrogate here.

Does the sponsor believe that TTR levels are an appropriate surrogate? And if so, among the individuals that did not appear to respond, at

least from the forest plot, were levels modified? They seem to have gone down in almost all patients, and yet some patients obviously through subgroup analysis did not appear to respond, so if they could comment on that.

The related follow-up question, then, is, was there any evidence that the sponsor has performed by way of analyses, biological or clinical, that there may be an added benefit of tafamidis and patisiran? And I understand that if it's biological, or at least by blood levels of TTR, obviously then it relates to the first question I asked; and if not, was there any clinical additive benefit of the two? Thank you.

MR. SLUGG: Yes. Thank you. So your questions relate to TTR reduction magnitude, the use of TTR as a surrogate, as well as any kind of biological correlation between the two. I'll invite my colleague, Dr. Vest, to address your question, but first, over 90 percent of patients received 75 percent or greater knockdown in TTR, so the drug is very robust as far as having consistent

deep and durable knockdown in patients with TTR amyloidosis. But let me have my colleague, Dr. Vest, address the rest of your question.

DR. THADHANI: Thank you.

DR. VEST: John Vest, Alnylam. As Dr. Slugg just indicated, we see near maximal TTR reduction of more than 5 percent in most patients, so it's a very narrow dynamic range for TTR reduction, and in that context, it's very difficult to discern the relationship between the magnitude of TTR suppression and clinical efficacy. The clinical efficacy endpoints are more dynamic, and they're impacted by numerous factors: disease severity, the age of the patient, the duration of treatment, et cetera, so it's really impossible to say for any given patient, for example, that that TTR reduction that they experienced on the study, it didn't lead to a clinical benefit. We just don't know where they were on their trajectory of decline, and we don't have an appropriate control for the individual patient to know what would have happened to them in the absence of treatment.

But based on the randomized comparison here, we see that the pharmacodynamic effect shows a benefit compared to placebo, which gives us the confidence that the drug is working by its mechanism of action, particularly because we've now seen this very consistently across two studies, both APOLLO-B and the original APOLLO study, where profound suppression of transthyretin has resulted in benefits on function, quality of life, cardiac laboratory parameters, echocardiographic parameters, all of which are very consistent between the two studies.

DR. THADHANI: And just to clarify, Dr. Butler, if I might, so therefore, you can't really use TTR, just given the complete knockdown, to demonstrate any evidence of an additive benefit of two agents over one per se. Then again to clarify, there was no clinical additive benefit of the two agents as evidenced by some of the measures you've shown. There was no analyses you've performed that demonstrates adding two agents to any patient would benefit them one over the other.

MR. SLUGG: Sure. Let me ask my colleague, Dr. Vest, to come back and address your question.

DR. VEST: John Vest, Alnylam. So we don't have anything that we can measure with tafamidis to assess its pharmacodynamic effect, so we're left with TTR reduction. There certainly, conceptually, biologically, a rationale to think you'll be suppressed on average by 85 percent or more, but that means there is 10 or 15 percent of transthyretin that may well benefit from being stabilized. So there's a sound biological rationale to think that the two would work synergistically.

Now with regard to the other part of your question about have we done any other analyses to look for this additive benefit, there's nothing, as I said, that we can do biochemically because we don't have anything to measure with tafamidis. Clinically, we shared with you previously, across our endpoint structure, when we look at the outcomes, we do see favorable trends with background tafamidis, but I would like to pass this

over to Dr. Witteles to speak further on the topic.

DR. WITTELES: Thank you. Ron Witteles. Thanks for that question. I would first emphasize that, of course, this trial was not designed to look at tafamidis plus patisiran. It's an important question, I think, if this drug is available, of how to use it. But ultimately, when I look at this trial, I look at it in the context of what did patisiran do for patients in the trial. Was it clinically meaningful? And to me, across these variety of metrics, it was.

Now, the question on the biologic plausibility, certainly that is very much there. Of course, tafamidis works as a stabilizer. Stabilizing actually raises transthyretin levels, and then the silencer of course is going to knock them down. They're orthogonal methods of action, and it's something that as a clinician, I would like the opportunity -- for two very safe and, I believe, two very effective drugs -- to be able to have that conversation with the patient about the risks and benefits of two drugs that work

differently but are both safe and effective for the disease.

DR. THADHANI: Thank you, and thank you, Dr. Butler. That ends my questions.

DR. BUTLER: Thank you, Dr. Thadhani.

Dr. Roy-Chaudhury?

DR. ROY-CHAUDHURY: Yes. Thank you, Dr. Butler. This is a question to the clinicians on the sponsor's side, and I would be very interested in having you all describe wearing an objective and as scientific hat as possible. I know we'll be hearing from patients later on, I'm presuming, but the question is, why do you think a 6-minute test of 14.7 meters with a baseline of 364 and a KCCQ of 3.7 from a baseline of 70 is, in fact, clinically meaningful, based on your experience over many years taking care of these patients?

MR. SLUGG: Thank you for your question, Dr. Roy-Chaudhury. Let me turn it over to Dr. Witteles to address your question.

DR. WITTELES: Ron Witteles. Thank you,

because that question really gets to the heart of the matter, I think. A number of us have used the term "inexorable decline," and I use that term very deliberately in this disease.

I remember when I saw the ATTR-ACT data first, and two things struck me. One, it was great to have a therapy for the disease; two was how consistent and linear that decline was in the placebo arm. This absolutely matches the years of experience I have treating patients with this disease, both before any therapies were available and after, where we've slowed the decline but not stopped it.

What that means to me, and when we look at the OLE data -- you can see it more; in fact, I'll pull this up -- that dashed line we expect to continue. And again, if you look at the ATTR-ACT data, we see the exact same thing, just with a steeper slope because it was done in an earlier era when patients were diagnosed later, but the consistency of decline is absolutely there.

What you see, of course, in the OLE is that

that stabilizes. Similarly, we see the same sort of thing with biomarker data. So when I see these 12-month endpoints of 15 meters and some odd difference, A, I do think that is clinically meaningful to patients, but, B, I know it's clinically meaningful when at 24 months I have every expectation that now it's 30 meters, and at 36 months, that gap is going to widen further, and so on and so forth.

The other thing I'd say when I look at this is that everyone who works in this space, one thing that they will consistently say is these parameters follow one another, and we see this from this trial and from other trial data. When you see NT-proBNP consistently being benefited, when you see troponin consistently being benefited, when you see KCCQ, when you see 6-minute walk, those hard outcomes I have every reason to believe would come the longer we follow patients. Recall that in ATTR-ACT, you wouldn't have seen the hard outcome difference at 12 months either. In fact, I would say we have more of a signal when I look at it here than you

would have seen at 12 months in ATTR-ACT.

So I think as I look at this data as a clinician, if I'm talking to a patient with a disease who's going to have a slope like this, and we can pretty clearly flatten that slope to what is really the age-related decline, that's something that matters, and I'm going to expect to only grow larger with time. Thank you.

DR. ROY-CHAUDHURY: Can I just ask a couple of very quick follow-up questions, if I may, Dr. Butler?

DR. BUTLER: Yes, please.

DR. ROY-CHAUDHURY: The first is, as technetium scanning becomes more and more widely used, the slope of that inexorable decline is going to become less and less. Does that factor into your earlier comments? Is 12 months really too small now to support the sort of use that I'm presuming you're anticipating?

DR. WITTELES: Ron Witteles. Thank you. It's a great question. I think the slope is smaller, but the relative benefit is not. So what

this trial clearly showed was, for the reason you cited about the technetium scanning, as well as just increased awareness of the disease, thankfully, the overall prognosis in this disease is better than it was at the time of ATTR-ACT. There's no question, and this matches clinical experience. However, the fact that it is an inexorable decline is not in question, and the data here shows that, and other contemporary trial data has shown the same thing.

So the fact that we can slow this decline by depending on the outcome that you're looking at, 60 and some odd percent, is absolutely really clinically meaningful, and with patients living longer, we expect that as you have curves diverging like this, those benefits are only going to accumulate and matter more over time.

DR. ROY-CHAUDHURY: Dr. Butler, if I may. This is very quick.

You mentioned a couple of areas where you, at a clinical level, would really like to use the combinations of people who haven't responded to

tafamidis, people with polyneuropathy and cardiomyopathy. Could you just expand on that? Are these the only two groups? Are there other groups that you think could benefit? Is there a patient that you really, really want to use this combination in your practice, and who is that patient?

I will stop there, and thank you, Dr. Butler, for allowing me to ask these questions.

DR. WITTELES: Ron Witteles. Thank you for that question. Yes, I think that there are multiple patients. Again, there's the first-line monotherapy for patients who have neuropathy and cardiomyopathy. This makes all the sense in the world. We have a drug that is clearly beneficial for both sides of the disease. But the second one I think is probably the one that would be most meaningful to many of my patients, which is patients who are on the only FDA-approved therapy right now, which is tafamidis, who have progressed, and there are a lot of these patients. I can't tell you how often I get the question, "Okay.

Well, what do I do if I get worse or I feel worse? What now?" And up until now, other than clinical trials that people can enroll in, the answer was, "Nothing." We didn't have something.

Well, now we have something that is clearly different, it works differently, and it's clearly safe, and we have, in my mind, clear efficacy data. So to deny a patient the opportunity to switch from an agent that they're progressing on to this safe and effective alternative therapy that works completely differently, to me, I would feel would be a real loss for the patients. I think the add-on to tafamidis is tougher, and I think everybody would acknowledge we don't have the data one way or the other, and yet it can theoretically make sense. But to be able to offer this to patients as a switch or to first line, if they have the mixed phenotype, makes a lot of sense.

The last point I'll make is that, as I mentioned before, to me, this is one disease. This is a disease of a transthyretin protein that misfolds and deposits in one tissue or the other.

And if I was a patient looking at the full totality of the data in the disease, and I know that the silencer in patisiran has been so much more effective for neuropathy than tafamidis was in its neuropathy trial, and I realize this is really one disease, again, I would like the opportunity to have the option of saying they are both effective in cardiomyopathy, but when I look at the totality of the disease, I actually think I want to try this one first. Thank you.

DR. BUTLER: Thank you, Dr. Witteles.

Dr. Bairey Merz?

DR. BAIREY MERZ: Thank you, Dr. Butler. Dr. Stockbridge's comment prompts another pretrial discussion question. Was there a discussion about what would be a lower bound of a clinically relevant change in a 6-minute walk test? Academics in a systematic review suggest that the range of minimal benefit would be 14-to-30.5 meters. Was this discussed at all, a lower limit of what might be considered a clinically relevant 6-minute walk test? Thank you, and any FDA person. Thank you.

MR. SLUGG: Sorry, Dr. Merz. Was that a question to the agency?

DR. BAIREY MERZ: To the agency. Thank you.

DR. SENATORE: Yes, I could initiate the comment that there was no previous discussion. But I would like to circle back the slide that was shown with regard to the extension and the dashed line showing progression of disease. We have a comment about that, and I would call on Dr. Stockbridge to come to provide that comment.

DR. STOCKBRIDGE: Yes. Could we have slide CO-77 back up? I just wanted to comment that it's really fortunate that we had the 12-month data to drive that dashed line through. If you were forced to drive that line through the points at 6 months and 9 months, you wouldn't have been able to conclude that there was any leveling off of the treatment effect after month 12 at all.

DR. BUTLER: Thank you, Dr. Stockbridge.

Dr. Bairey Merz, do you have any follow-up questions?

DR. BAIREY MERZ: That actually

didn't -- let me clarify. And again, it's to the agency, and maybe I did hear the answer. There was no discussion of what would be a clinically relevant minimal change for lower bound on the 6-minute walk test. There was no pre-discussion about that.

DR. SENATORE: That is correct. There was no pre-discussion about that. We simply stated that we would like to see a clinically meaningful benefit. What we did not mention, what we have in mind, are things like 30 meters, what was shown in tafamidis and in other clinical trials where 6-minute walking distance was the primary endpoint.

DR. BAIREY MERZ: Thank you, Dr. Butler.

DR. BUTLER: Thank you, Dr. Bairey Merz.

Dr. Peterson?

DR. PETERSON: Yes. This is a follow-up to the sponsor with regards to the design, and it gets at the last question by Dr. Bairey Merz. The sample size calculations for the study when it was originally designed predisposed, at least according to the FDA comments, a larger effect size for both

the 6-minute walk and the change in its primary secondary outcome.

Do you want to comment? Do you have any rationale, or reasons, or explanations that you would want to put forth, hypotheses, about why the effect size seen in the actual study was less significant than you had anticipated in the study design in terms of the sample size?

MR. SLUGG: Yes. Let me have my colleague, Dr. Vest, address your question.

DR. VEST: John Vest, Alnylam. So when we see, for both 6-minute walk test and KCCQ, that we are achieving stability, or relative stability, the magnitude of the effect is entirely determined by the decline on the placebo arm. And for the patients that came into this study -- as we highlighted during the presentation, and as Dr. Witteles has talked about, and Dr. Berk, in their clinical experience -- the patients are just not as advanced in their disease now as they were in the era of ATTR-ACT, and this is highlighted both in the baseline characteristics of these

patients.

We can see here, in New York Heart Association III, 7 percent of patients versus 35 percent on ATTR-ACT, and they're over 1000 nanogram per liter difference in NT-proBNP. But really more importantly, as illustrated by the relative decline on the two placebo arms, which is shown at the bottom of the figure, and then will show graphically here, the decline on the APOLLO-B placebo arm, as you can see, we're comparing means 29 meters versus the precipitous decline of almost 60 meters on the ATTR-ACT study. So our treatment effect is bound by that placebo decline when we've achieved the very high bar, clinically, of maintaining stability in these patients.

So that would be my response with regard to the magnitude of effect. I'd also just like to show the same message with KCCQ, which we're showing here. Again, we saw there was a precipitous decline on ATTR-ACT in these very advanced patients of 10 points, whereas the patients in APOLLO-B, who are just earlier in the

disease course, had a decline of 3.4 points, but the same message. We achieved stability, so that bound the magnitude of the effect that we could demonstrate.

DR. PETERSON: Sorry. If I could have just a quick follow-up, the first of which is that I think you got into the study the patients of the appropriate class that you wanted to in your design, and you knew the data of where they were and the status of their disease when you designed the study. You targeted it towards earlier patients. And then number two is, at least the data we have so far in the subgroup analysis of that small sample size, there wasn't an effect differential by the degree of severity of the patients entering this study, so it doesn't necessarily track that the treatment effects you're seeing are less treatment effects, much smaller treatment effects, and you imagined in your sample size would carry through.

DR. VEST: I want to make sure I understand the -- could I just ask you to clarify the

question? I'm sorry.

DR. PETERSON: Sure. First, when you did your sample size calculations, you didn't base them truly on ATTR-ACT only because you had an idea, the fact that you were going to target people who were in less severe disease state and earlier in the disease state than in the prior trial. So that would just mean you should have potentially anticipated a smaller delta in therapy at 12 months in the placebo arm.

The second idea was that if you're saying it's because you had your class of I and II patients, then you should have seen a slightly smaller treatment effect in those populations. You don't see that in this study. If anything, the treatment effects are at least as big in that population, if not bigger, than seen in the people in New York Heart Association class III, if I recall the data.

DR. VEST: Yes. I'm going to pass this over to Dr. Silliman, who's going to help to address your question.

DR. SILLIMAN: Nancy Silliman, Alnylam. Just to clarify, in ATTR-ACT, they saw a similar decline in the placebo for NYHA class I-II versus class III, so we did design our patient population to be healthier because we needed them to be able to -- well, we were hoping they could do the 6-minute walk test at month 12. But we did use the information that we had from ATTR-ACT, so we were expecting the larger absolute difference, and then it's really just the change in the patient population that we've been talking about. But importantly, we do see a very similar relative effect.

DR. BUTLER: Dr. Peterson, any further clarifications?

DR. PETERSON: No further questions. Thank you.

DR. BUTLER: Great. Well, thank you very much.

So we are almost at the lunch time, actually a few minutes over. I would like to give the applicant an opportunity -- there was one more

question regarding the biological effects, especially BNP by tafamidis and no tafamidis. I'm going to assume that you don't have that data just yet, and we can look at it after lunch, but in case if you have it, we can present it now.

MR. SLUGG: Yes. We have the data. We're unable to share it at this point to you, but there was, I think, a prior comment around the relative percent reduction of the patients over time, and we do have some information relative to the 10 percent change relative to baseline, because a lot of the questions were circulating around what the proportion of change is relative to the baseline, and if that's meaningful. And we have the analyses that have shown the change relative to the patient baseline, which might be informative to the discussions that have been had here today, and Dr. Vest can walk you through those.

DR. BUTLER: Let's take two quick minutes to do that, and then we'll need to break for lunch.

MR. SLUGG: Thank you.

DR. VEST: John Vest, Alnylam. Yes, to

address the issue around the percent change from baseline, we did look at thresholds of change from baseline, and what prompted this analysis was a 2022 consensus statement in the Journal of the American College of Cardiology Heart Failure that included academics from both the U.S. and Europe, the FDA, and other stakeholders. It was suggested in there that a 10 percent change from baseline, which inherently accounts for each individual patient's baseline, could be clinically meaningful. So we considered that as a threshold, and I'm showing that here.

As you can see, it's consistent with the data we showed during the core, and we see that the best results are more common in patisiran patients who improved by that threshold, and the worse results are more common in placebo patients who declined by that threshold, which the consensus statement suggested should be considered as clinically meaningful.

DR. BUTLER: Well, thank you very much.

We will conclude this session at this point,

and we will now break for lunch. We will reconvene at 1:30 pm Eastern Time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to reconvene at 1:20 to ensure that you're connected before we reconvene at 1:30 pm. Thank you very much.

A F T E R N O O N S E S S I O N

(1:30 p.m.)

Open Public Hearing

DR. BUTLER: Welcome back. It is 130, and we will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the applicant. For example, this financial information may include the applicant's payment for your travel, lodging, or other expenses in connection with your participation in this meeting.

Likewise, FDA encourages you, at the

beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation. Also, we have many who will be speaking at the open public hearing, and each speaker will have 3 minutes. If at the end of your 3 minutes time,

if I interrupt, please realize that no disrespect is intended.

With that speaker number 1, please unmute and turn on your webcam. Please introduce yourself. State your name and any organization you're representing for the record. You have 3 minutes.

MS. FINKEL: Thank you. My name is Muriel Finkel. I have no financial disclosure. I am founder and president of Amyloidosis Support Groups. We are a 501(c)(3) nonprofit and have been dedicated to the education, empowerment, and support of amyloidosis patients and their loved ones since 2005. We meet in 30 cities, and with the help of amyloidosis physicians have helped more than 8,000 amyloidosis patients and caregivers at our in-person meetings and webinars.

ONPATTRO was approved for hereditary ATTR with polyneuropathy in 2018, and our patients with ATTR with polyneuropathy tell us that ONPATTRO has been a game-changer for them. Many watched a parent become disabled from amyloidosis before

there were treatments available. They witnessed their neuropathy forced them from canes, to walkers, to wheelchairs, and their bowel and stomach issues forced them into diapers and agoraphobia. Many saw their loved ones waste away to a painful and undignified death.

We do have one treatment that is approved for ATTR cardiomyopathy, tafamidis, also known as Vyndaqel and Vyndamax. It is a pill which is covered under Medicare Part D as in David. Since most patients with wild-type form of ATTR are over 65, Medicare coverage plays a huge part in their ability to access necessary medications. As you likely know, there is no out-of-pocket maximum in Medicare Part D, and even 5 percent of this medication is a huge out-of-pocket expense. There is help for those meeting the various poverty level guidelines, but for many retired individuals, the cost can be $2,000 a month or more. Some patients have told us they would rather opt for no treatment rather than put their families in financial ruin.

Today we are asking you to approve ONPATTRO

for the many ATTR patients who are suffering with a cardiomyopathy. ONPATTRO is administered by infusion and would be covered under Medicare Part B as in boy. This would mean that patients can be protected by their Medigap plan or the out-of-pocket maximum and Medicare Advantage Part C plans. If approved, ONPATTRO would provide an option to those patients and their physicians who do not wish to prescribe tafamidis.

We do have ATTR patients with cardiomyopathy already on ONPATTRO. Some are on clinical trials. Some were diagnosed with hereditary ATTR with polyneuropathy prior to their cardiomyopathy being diagnosed. They have told us how lucky they feel to have been in on the ground floor of what they feel is a life-changing treatment.

Without a neuropathy diagnosis, insurance companies will not now cover ONPATTRO. Our cardiac ATTR patients need this treatment. They don't need more barriers. They've broken down the largest barrier of all, the barrier to get a diagnosis. The next step should be access to all treatments

that might extend their life and improve their quality of life while allowing them to avoid financial ruin. Please approve ONPATTRO for ATTR with cardiomyopathy. Thank you.

DR. BUTLER: Thank you very much.

Speaker number 2, please unmute and turn on your webcam and introduce yourself. Please state your name and any organization you're representing for our record. You have 3 minutes.

MS. BOEDICKER: I'd like to thank the committee for the opportunity to speak today. I have no financial disclosure to report. My name is Deborah Boedicker, and I am here on behalf of Mackenzie's Mission, a nonprofit whose mission is to make a difference in the fight against amyloidosis.

My daughter, Mackenzie, was diagnosed with amyloidosis 6 years ago at age 23. At that time, there were no FDA-approved treatments, and the universe of knowledgeable healthcare experts was limited, and the life expectancy was 12-to-18 months post-diagnosis. There was a

massive unmet need for patient care. Since then, Mackenzie's Mission has developed an educational initiative where we work with amyloidosis cardiomyopathy patients who serve as patient educators to raise awareness within the healthcare community, thereby accelerating diagnosis and the start of treatment, leading to improved patient lives.

Cardiomyopathy has a life-changing impact on patient's lives, and this can be seen in many ways, so I offer just four examples. One, extreme fatigue, to the point where patients have difficulty walking from the bedroom to the bathroom, traversing the aisles of the grocery store, or up a flight of stairs, and this disease impairs everyday tasks that most of us take for granted;

Two, the inability to be active, such as riding a bike or walking, patients lose the ability to participate in a physically active life;

Three, emotional toll. Patients with cardiomyopathy are acutely aware that their heart

doesn't function properly, a fear which imposes an exhaustive, depressing, and invisible burden on their mental health;

Number four, life revolves around their disease. Patients' lives are no longer driven by normal living but by their disease. Between treatment, recovery, testing, and meetings with their healthcare team, life must adjust to accommodate their disease journey.

So while there is an approved treatment, that is not enough for healthcare providers to meet the broad spectrum of amyloidosis cardiomyopathy patient needs. Patients are seeking more treatment options, options that can work with their lives today and ease the impact of this disease. This disease is a journey for patients that has no cure. The availability of more approved treatments like the one you are reviewing today could alter their course of their patient journey in a much improved way. Thank you.

DR. BUTLER: Thank you very much.

Speaker number 3, please unmute and turn on

your webcam and introduce yourself. Please state your name and any organization you're representing for the record. You have 3 minutes.

DR. SARSWAT: My name is Nitasha Sarswat. I'm an advanced heart failure and transplant cardiologist at the University of Chicago and NorthShore Hospital Systems. I have a particular interest and passion for amyloidosis. I've been practicing advanced heart failure for about 10 years, and started the amyloid program when I came to University of Chicago in 2015, though I've been heavily involved in the field prior to that. I've been involved in many of the TTR clinical trials through the years, including registries and stabilizers, and siRNA therapies.

While we know that this drug has already been approved for hereditary neuropathy, I strongly believe that this is all one disease regardless of whether the manifestation is cardiac or neurologic. We have already seen a significant improvement in our patients' lives with neuropathy alone and in those with both cardiomyopathy and neuropathy. I'm

also involved in the amyloidosis support group and hear from patients all over the country, not just in Chicagoland. As an amyloidosis specialist, both the patients and I are really excited to have another way to treat this disease that will improve their quality of life.

Additionally, as a cardiologist, the idea that the drug actually improves blood flow to the body and potentially end-organ function is a very exciting one. These patients want to be able to run after their grandchildren and go for walks. We need another treatment for patients to attack this disease from the initial point, as this disease causes such morbidity and mortality.

I've had several patients in the APOLLO-B trial and in the early access patisiran trial that have really attributed their ability to go on vacations, stay out of the hospital, and be more active. I have a particular 74-year-old patient, male, who was having trouble visiting his wife in a rehab facility after her hip fracture. Once he started the early access program, he's been able to

make it there. He's been able to walk, see her, and enjoy their life together, and help her recover.

This is the case for patients, in general, who have all felt better on patisiran. Patisiran has been generally well tolerated, and most patients are very eager to be able to access the medication. I have a list of patients that will be calling me on October 8th, eagerly awaiting the FDA decision. Thank you for your time.

DR. BUTLER: Thank you very much.

Will speaker number 4 please unmute and turn on your webcam? Introduce yourself, including your name and any organization that you're representing. for the record. You have 3 minutes.

MR. GIGLIO: Good afternoon. My name is Ozzie Giglio. I represent no organization other than myself, and I have no financial disclosures or relationships.

DR. BUTLER: If possible, can you turn on your webcam? Thank you.

MR. GIGLIO: Thank you. I am 62 years old.

I spent over 30 years in the United States Navy, and now retired. I deployed multiple times to Iraq, Afghanistan, and numerous other places throughout the globe. I've been a lifetime athlete, a volunteer firefighter, and an avid motorcycle enthusiast. My careers and hobbies always demanded that I maintain the highest levels of physical standards. I'm now the CEO of a family business headquartered in Chicago, with operations in multiple states and 400 plus employees. I have a phenomenal bride of 23-plus years. We have two beautiful children, twins, that are age 6. We reside in a wonderful suburb of Chicago.

Unlike many other amyloidosis patients, I discovered my amyloidosis in a rather random fashion. In January of 2015, I went to the Mayo for a two-day comprehensive physical exam. I had no remarkable issues to speak of, other than an ever slight decrease in my physical performance levels. I was completely asymptomatic, or at least that is how I perceived it. I received a PYP exam, and in June of 2015 found out I had wild-type

amyloidosis. The doctors prescribed diflunisal, which really only would be slowing my ultimate early demise.

Over the next year or so, I could actually feel a little bit of a decline. I became an avid reader on the disease and attended a number of sessions of the Amyloidosis Foundation, which were always extremely informative. I believe it was some time in 2017 I was placed on tafamidis and remain on it today, and then about 30 months ago, I was introduced and was able to get into a study for patisiran.

My experience with patisiran has been essentially seamless. I've never had any adverse reaction to the drug, and because I'm very plugged into my body and performance, I would argue vehemently that the drug is working, and there's without a doubt in my mind preventing any further deterioration, and I believe it is actually improving my performance levels. I cover at least 6 miles running, I do 400 stairs, and 400 pushups a day. I do not feel fatigued or any other

significant symptoms.

Our family leads a generally normal life, and together we try not to let this get us down, but the disease and its impact on my heart does impose a burden with visits to doctors and attention to my battle with the disease. With cardiac amyloidosis, you generally get a a short five-year post-diagnosis life expectancy. Historically, there have been little to no treatments to prevent the disease from progressing other than the extreme measures such as heart or combined heart and liver transplants. With patisiran, there could now be a drug available to interdict the disease, and although not a cure per se, my story shows the therapeutic impact it can have to slow the progress of the disease.

So please remember my story and the others you are hearing today as you consider the decision. What this treatment means for me and other patients who need this option is hope, promise, and most importantly, time. Thank you for your time and attention today.

DR. BUTLER: Thank you very much.

Will speaker number 4 [sic] please unmute and turn on your webcam? Introduce yourself, including your name and organization that you might be representing for the record. You have 3 minutes.

(No response.)

Speaker number 5?

MR. MARKO: I'm here.

DR. BUTLER: Yes.

MR. MARKO: You said 4.

DR. BUTLER: My apologies.

MR. MARKO: Hello. My name is Steve Marko. I'm 75 years old and married for the past 50 years to my supportive wife, Susan. I have no financial disclosure. I was diagnosed in 2015 by the Mayo Clinic Lab through a heart biopsy and gene sequencing evaluation that verified that I have ATTR amyloidosis, wild type, with cardiomyopathy.

My symptoms began at age 57. In 2005, I had 4 trigger fingers, two on each hand. In 2006, I had carpal tunnel on both hands. In 2007, I had

pericardial infusion, and in 2019, I developed severe spinal stenosis, which were all alleviated through surgical procedures. I've had progressive neuropathy in both feet, multiple cardioversions to alleviate atrial fabricated [sic], and constant atrial fibrillation starting in 2019.

In 2019, for the doctors at Boston Medical Center Amyloidosis Clinic, I was told that the non-FDA approved drug, diflunisal, for the treatment of amyloidosis that I had been taking since 2015 was losing its effectiveness on me. In August of 2020, I applied for and was accepted to the APOLLO-B phase 3 clinical trial, and I've committed to being a trial participant for four years.

I was told this past year by my Boston Medical Center study doctor, Dr. John Berk, that I have actually been receiving the study drug, patisiran, beginning with my first infusion in September of 2020. I continue to receive my infusions, and actually had one yesterday, and I can tell you that I've never had an adverse

reaction to the study drug or the pre-meds in the three years I've been in the trial, nor any issue with the infusion physical process by the Boston University School of Medicine Research Unit staff, where I've had all infusions and evaluations.

I'm also very happy to share with you that my physical activity has not declined for the three years I've been in the clinical trial. I've rejoined our fitness center in January of this year after the COVID shut down, and go there 3-to-4 times per week, with elliptical cardio workouts at 60 minutes and approximately 2-and-a-half miles. I've noticed improvement in climbing stairs and consistency, and all eight of my 6-minute walk tests are approximately 460 meters.

In July of 2021, I had an upper body EMG evaluation conducted as a baseline evaluation and had another upper body EMG evaluation in May 2023. Results for the evaluation doctors were there has been no change. I also had a bone density evaluation in January of 2021, and again in May of 2023. Results are I had normal bone mass.

Staying active is very important to me. Although I retired 10 years ago, I've been very active my entire life, raising five children, hunting, fishing, camping, building a home, and caring for two horses. I've been a member of the --

DR. BUTLER: I very much appreciate it, but we are a little bit over 3 minutes. May I request you to conclude?

MR. MARKO: Alright. Just the last thing. My current life goal is to see our 11-year-old granddaughter, whom my wife and I adopted in 2022, off to college. For someone diagnosed with my condition years ago, this goal would not have been possible, but today I believe it is possible with the drug you have in front of you. I am just one person. This is just my experience, but I hope it helps you understand the difference it can make in one person's life and all the lives it touches. I represent so many out there who need --

DR. BUTLER: Thank you.

MR. MARKO: -- treatment options like this

one. Please think of me, and thank you.

DR. BUTLER: Thank you so much.

Will speaker number 6 please turn on your webcam and introduce yourself? State your name and any organization you might represent. You have 3 minutes.

DR. HUNG: I'm Rebecca Hung. I am a heart failure cardiologist at Vanderbilt and have been a member of the Vanderbilt Multidisciplinary Amyloidosis program for over 10 years. I am the site PI for APOLLO-B, but have no other financial disclosures.

Vanderbilt is a major regional center for amyloidosis, both AL and TTR, and sees patients from 12 states in the Southeast. At Vanderbilt, we have a panel of over 240 TTR patients, including gene carriers that we follow. We serially track biomarkers and pre-albumin levels, and then all our ambulatory patients collect 6-minute walk data. We enrolled 15 patients in APOLLO-B in its early access program. We deliberately chose to enroll wild-type patients because variant patients often

qualify for silencing therapy under the neuropathy indication.

Of our initial 5 patients, all ambulatory NYHA II at enrollment, three were randomized to placebo. Of those three, two have died directly related to TTR, and the third is struggling. The two randomized to patisiran both had atrial arrhythmias that required ablations but remain both ambulatory with relatively preserved 6-minute walk, BNP, and renal function.

As part of the expanded access program, we added 8 patients who met criteria for progression of disease by symptoms, biomarkers or worsening LV function, while on tafamidis. I recently saw one of those patients, a 79-year-old man in follow-up. He and his wife drive from Indiana to Nashville for his infusions. They felt he had no quality of life on standard-of-care tafamidis. His wife told me, unprompted two weeks ago, "I think the infusions saved his life."

Prior to coming to Vanderbilt, he was hospitalized almost biweekly for heart failure.

Since starting patisiran, he has required no augmentation in his maintenance diuretic and has had no readmissions for heart failure. He is more active, although obviously still limited, but doing things he and his wife report that he could not do two years ago. His most recent proBNP was at its all-time low, and his 6-minute walk remains preserved over the 16 months that we have been seeing him.

Another patient of mine presented 4 years ago at age 77 with second degree AV block, needing a pacemaker. The year before, he was biking regularly and could climb the stairs at Percy Warner Park. He could not regain that level of function after the pacemaker. He received tafamidis early as part of the ATTR-ACT expanded access program. On his first 6-minute walk in 2019, he covered 1360 feet. By last summer, that had dropped to 1200 feet, which might be explained by the natural history of aging. Last October, he started patisiran. At his most recent visit, the 6-minute walk was back up to 1400 feet and he had

resumed climbing the stairs at Percy Warner.

At Vanderbilt, we have observed the expected decline in 6-minute walk and quality of life that continues to be the natural history of TTR cardiomyopathy, even on tafamidis. Our patients, in an, albeit, non-randomized and unblinded fashion, had seen additional stabilization or improvement in symptoms and quality of life with the addition of patisiran with no significant adverse effects. Thank you.

DR. BUTLER: Thank you so much.

Will speaker 7 please unmute and turn on your webcam? Introduce yourself, stating your name and any organization that you might be representing. You have 3 minutes.

(No response.)

DR. BUTLER: This is for speaker 7.

(No response.)

DR. BUTLER: You're muted, sir. We can't hear you. Great.

MR. ZIMMERMAN: Hello, everyone. My name is Bob Zimmerman. I have no financial interest in

this session whatsoever. I've been married to my wife, Pat, for 59 years. We have two grown children and four grandchildren. A Rutgers 1961 graduate, Navy-trained carrier pilot, I was hired by American Airlines, where I flew for 32 years, retiring as an international captain on the 767. I continued to fly a Cessna 182 until 2015 when I could no longer pass a physical exam because of an abnormal EKG.

After 2015, under the care of then Dr. Hasan Garan, chief of electrophysiology at Columbia Presbyterian Hospital, I was diagnosed with non-sustained ventricular tachycardia, eventually cardiomyopathy, followed by atrial fibrillation. I've had an angiogram, an ablation, numerous echocardiograms, and three cardiac reversions to regain a normal sinus rhythm, all to no avail. My ejection fraction had slumped to 20-to-30 percent. I received an ICD in 2019.

At the end of May of 2022, I was diagnosed with wild-type ATTR, stage 3 cardiac amyloidosis by Dr. Gabriel Sayer at Columbia, who recommended me

to Dr. Mathew Maurer, who was beginning Alnylam's APOLLO-B study at Columbia Presbyterian Hospital of patisiran. My first infusion was November 30, 2022. Dr. Maurer told me it would be 6-to-9 months before I felt any change. I think he was spot-on. During those first months, just a short walk from the car for a restaurant meal or for shopping would make me very tired. I used the wheelchair in the hospital and at the airport.

Around my 13th infusion, between June and July, I began to notice a difference in my energy level. I could now walk 5-to-10 minutes without looking for a place to sit. I began doing some activities around the house, like taking out the recycling to the curb and sweeping out the garage. I spent time at the gym, walking up to 10 minutes before resting. My wife walked with me around our streets and town for about 10 minutes one way, and back for another 10 minutes to the house. My pace on the Apple watch was 2-to 2-and-a-half miles per hour, total time about 20 minutes.

I can now do regular shopping at our local

supermarket for 30-to-45 minutes it takes to get around the store and not feel tired at the end. I'll do a Costco run easily. I've ridden a bicycle a few blocks, then to the gym for very light workouts, and even threatened my golf clubs with a good stare. All this may not seem terribly exciting, but those infusions have given me my life back with an outlook much better than it was a year ago. That's what I believe you can do today for the many other patients out there who are in desperate need of another option. You can give them the hope of a better outlook on life with this treatment. Thank you for your consideration.

DR. BUTLER: Thank you so much.

Will speaker number 8 please unmute and turn on your webcam? Introduce yourself, your name, and any organization that you might be representing. You have 3 minutes.

MR. MAYWEATHER: Good afternoon. I don't represent anyone other than myself, and I have no financial disclosures to announce. My name is William Mayweather. I'm here today as living proof

of the incredible impact that a groundbreaking drug can have on individuals and families. I'm a husband, married for 32 years next Thursday, and a father of three grown children. We've raised our family in Robbinsville, New Jersey, nestled near Princeton University, equal distance between New York City and Philadelphia.

I believe that the FDA and Alnylam, through patisiran, have the potential to bring immediate hope to thousands. I believe because the drug has positively changed my life and my family's. Patisiran has given me a new lease on life. At 59 years old, my life has had many twists and turns, but it's the journey with my heart condition that I want to share today.

My heart journey began with a history of syncope. At 16, while playing elite level soccer, I passed out. Over time, my heart's rhythm wasn't quite right, leading to a diagnosis of sinus node dysfunction. This marked the start of my relationship with pacemakers, with the first one implanted in 1988. Over the years, I had upgrades,

including a dual-chamber pacemaker in 2017. During this time, my heart's wall thickened, and the doctor suspected hypertrophic cardiomyopathy, HCM. By 2017, my energy levels and my exercise tolerance were dropping. The emotional burden on my family was palpable as they watched me grapple with worsening symptoms.

The suspicion of HCM led me to Penn Medicine's Heart and Vascular Center. After a year of investigation, including echocardiograms, a heart MRI, a fat pad biopsy, a heart biopsy with mass spectroscopic analysis and genetic screening, in 2018 I was diagnosed with ATTR-CM, caused by a Val 122 allele transthyretin protein abnormality.

In 2018, ATTR-CM had a reputation for being fatally progressive, pushing individuals like me toward the inevitable need for a heart and liver transplant to delay death. Each medical report painted a somber picture of my heart's decline, burdening my family. Desperate, I challenged my medical team to not only keep me alive, but halt the downward spiral. This marked the beginning of

my journey to patisiran.

Incorporating patisiran into my treatment regime changed the medical reports, showing stability in my heart's performance. For me, patisiran halted the march of ATTR-CM. While some exercises leave me winded, the daily energy I experience is a testament to medical innovation and the drug's efficacy. Patisiran's impact reaches far. My family, once witness to my struggle, now sees my revival. For me, patisiran is not just a drug; it's hope and a lifeline to our family's future.

In closing, I am grateful to the FDA considering my story. You stand at the intersection of science and compassion. Each approval signifies not just scientific achievement, but hope, a lifeline to individuals and families. Thank you for your dedication to making a difference in lives like mine.

DR. BUTLER: Thank you very much.

Will speaker number 9 please unmute and turn on your webcam? Introduce yourself, including your

name and any organization that you might be representing. You have 3 minutes.

MR. GERTH: Good afternoon. I have no financial disclosures. My name is Charlie Gerth, and I'm representing myself. I am 84 years young and a U.S. Navy veteran. I've been married for 43 years, have three grown children from a prior marriage, 5 grandchildren, and one great grandchild. I live in Phoenixville, Pennsylvania, 3 miles west of Valley Forge National Park, where I am a fire police first responder in the Valley Forge Volunteer Fire Company.

I have always been a high-energy person with a love of travel and the great outdoors; however, in the summer of 2021, I noticed that my energy levels were falling off somewhat and thought perhaps I was just getting old. In November of '21, I was diagnosed with smoldering MGUS, and in December, after the onset of afib, an echocardiogram showed I had low heart functionality, as well as heart muscle thickening.

A follow-up heart biopsy in February of 2022

revealed I had amyloid deposition. Despite the presence of MGUS, my hematologist suspected I had ATTR-CM rather than AL amyloidosis. Subsequent amyloid typing at the Mayo Clinic confirmed the CM diagnosis, and genetic testing indicated I had the wild-type barrier. In March of '22, my amyloid cardiologist prescribed tafamidis to treat my ATTR, and in May, I underwent a cardioversion to restore my heart to sinus rhythm. Six weeks later, a series of blackouts sent me back to the hospital, where they discovered I had severe bradycardia and a high-grade heart block. Two days later, I had a biventricular pacemaker implanted in my chest.

In December of '22, while visiting my amyloid cardiologist, I learned about patisiran and the expanded access protocol that offered patisiran to selected patients with wild-type ATTR-CM. The clinical trial results sounded promising, so I applied for participation in the EAP. Thus far, I have received 6 patisiran infusions without any side effects, either pre- or post-infusion.

These days, my energy levels have returned

to the point where I am walking 3-to-4 miles every day, and I have no typical ATTR symptoms such as shortness of breath, chest pains, et cetera. Bottom line, I feel great. The combination of tafamidis and patisiran, along with my pacemaker, gives me the brightest hope for the future. I am extremely thankful to have these options available to me for treating and slowing my disease progression. I hope by sharing my story, you will come to understand the need for multiple ATTR treatment options, including patisiran, to be available for people like me who have this life-altering condition. Thank you for listening.

DR. BUTLER: Thank you very much.

May I request speaker number 10 to please unmute, turn on your webcam, and introduce your name and any organization that you might be representing? You have 3 minutes.

MS. BECKWITH STANLEY: I'm not representing any organization, and I have no financial disclosures. My name is Cecelia Beckwith Stanley. I'm 73 years old. I live in Portland, Oregon with

my husband. I have two wonderful children and an incredible grandchild. Prior to being diagnosed with hereditary amyloidosis, I was a nurse practitioner working in medically underserved patients.

ATTR is a systemic disease, and approximately 80 percent of people present with both cardiomyopathy and polyneuropathy, and I am one of those individuals. I've been navigating the debilitating symptoms of hereditary amyloidosis for 18 years. In 2010, I was diagnosed with heart failure after cardiac biopsy, and it was determined I had amyloidosis. I traveled to a center of excellence, was diagnosed with hereditary amyloidosis due to the V122I genetic variant, and it was labeled as a cardiac form of hereditary amyloidosis. This was confusing to me since my initial symptoms were neurological and they continued to persist. Less than one year later, I was a candidate for a heart transplant. On August 8, 2012, I received a new heart. My life improved immensely. I no longer experienced

symptoms of heart failure.

You know, my heart transplant has changed how we live as a family. I'm at risk for infectious diseases, every infectious disease I come in contact with, as well as certain types of cancer. Leaving the workforce 10 years before planned places an extra burden on my husband. If patisiran had been available 18 years ago, I would not have needed a heart transplant. I would not have suffered through the extreme pain for years of not knowing why I had bilateral carpal tunnel, polyneuropathy, and chronic constipation. This treatment can significantly improve the quality of life and prevent the debilitating symptoms of hereditary amyloidosis.

I am a part of a network of heart transplant patients with the V122I genetic variant. Everyone is receiving patisiran, and they continue to report that their quality of life has improved significantly because of a decrease of neuropathy, as well as easing the worry about amyloid depositing in their hearts.

The V122I genetic variant has a 4 percent prevalence in the African American community, putting almost 200,000 people over the age of 65 at risk for hereditary amyloidosis. We are in need of treatment options. We would all benefit if the systemic nature of hereditary amyloidosis was better understood. Hereditary amyloidosis is one disease. Early diagnosis should be the norm, with access to all life-saving treatments to support the overall improvement of the quality of our lives. Thank you very much for giving me your time and listening to me. I appreciate it.

DR. BUTLER: Thank you very much.

May I request speaker number 11 to please unmute and turn on your webcam, and introduce your name and any organization you might be representing? You have 3 minutes.

MS. COOPER: Good afternoon, and thank you for allowing me time to address the committee. My name is Josie Cooper, and I'm here today in my role as executive director of the Alliance for Patient Access. Alnylam is one of several supporters of

AFPA's work. The Alliance for Patient Access is a national network of policy-minded healthcare providers who advocate for patient-centered care. We support health policies that reinforce clinical decision making, promote personalized care, and protect the physician-patient relationship.

We also host a rare diseases working group, which brings together amyloidosis specialists to ensure that clinician perspectives are heard as decisions impacting patient care are being made. We represent physicians, nurse practitioners, genetic counselors, and other clinicians treating both cardiac and neurologic presentations of the disease.

Transthyretin amyloidosis is a rare disease caused by the buildup of abnormal protein in different organs, and as others have already shared, this disease comes with a range of debilitating symptoms and very considerable patient burden, both physical, as well as mental. It's a progressive disease, and left untreated can be fatal. Cardiac amyloidosis can lead to decreasing

heart function, fatigue, shortness of breath, and ultimately heart failure. That makes early diagnosis and effective treatment critical.

While we are very pleased that several FDA-approved medications are available for amyloidosis, currently, just one of those is for amyloidosis-related cardiomyopathy. That means that additional FDA treatment options, particularly for cardiac amyloidosis, are really critical in ensuring that clinicians and patients have the maximal opportunities to successfully treat this disease.

As FDA considers an additional indication of cardiac amyloidosis for patisiran, we urge you to prioritize the unmet need that is still faced by this community. While AFPA does not offer comment on the clinical effectiveness of patisiran for cardiomyopathy, we ask the committee to bear in mind the significant burden of amyloidosis on patients, on families, and on communities, an opportunity that an additional treatment option would provide.

Another treatment option for cardiac amyloidosis would prove valuable for patients, particularly as patisiran offers a different method of administration for patients, and having for the first time multiple treatment options for cardiac amyloidosis would also benefit providers, including those represented by AFPA, by allowing clinicians to have an additional treatment tool for this disease. So on behalf of the Alliance for Patient Access and our members, we urge you to strongly consider an sNDA for patisiran in order to support patients living with this disease. Thank you for your time.

DR. BUTLER: Thank you very much.

May I request speaker number 12 to please turn on your webcam, and state your name and organization that you might be representing? You have 3 minutes.

MR. RILEY: Hi. I have no financial disclosures to present. I am a patient, a volunteer patient educator for the Amyloidosis Speakers Bureau. My name is Sean Riley. I'm

60 years old, and I live in New Hampshire with my lovely wife, Robin. After working for 30 years as a nuclear reactor operator, I had to retire out of necessity due to degrading health associated with hereditary transthyretin amyloidosis, specifically the T60 mutation.

I must tell you that it can be extremely challenging for me to talk about my amyloidosis journey, very emotional. During the time period leading up to diagnosis, my physical health was spiraling downward. I firmly believe that the therapeutic results that I've gotten from patisiran have literally saved my life.

I was diagnosed in early 2019, following a 6-to-7 year struggle with steadily increasing disease symptoms. At the time of my diagnosis, I was extremely orthostatic, had minimal cardiac endurance, and had severe muscle loss in my legs due to polyneuropathy. When the doctor gave me my diagnosis, he explained to me the gravity of the situation and suggested that I start treatment with patisiran. I was advised that without the drug, my

condition would likely be terminal in 2-to-3 years. I literally would not be here today speaking to you without patisiran.

I started on patisiran in May of 2019 and recently received my 68th treatment. I can tell you from my own personal perspective the treatments have not only halted the disease progression but have allowed for significant improvement in my overall health. Just prior to starting treatment, I had an echocardio test. Quoting the summary note from the test, "There is a moderate-to-severe increase in left ventricle thickness." A more recent test result noted that there appeared to be no additional degradation in my cardiac condition.

These findings match with my daily life experience. I have noticed increased cardiac endurance and the ability to become more mobile. I am now able to walk upwards of a mile on flat terrain. Additionally, my orthostatic symptoms have become significantly more manageable. Again, I've had 68 treatments with patisiran. This drug has literally saved my life. I strongly urge the

FDA to look upon the patisiran APOLLO-B phase 3 results favorably, as they back up the results of my own experience. Thank you very much for your time.

DR. BUTLER: Thank you very much.

May I request speaker 13 to please unmute and turn on your webcam? Introduce yourself with your name and any organization that you might be representing. You have 3 minutes.

MR. MALLON: Aloha. My name is Peter Mallon. I am 64 years old and live in Hawaii. I have no financial disclosures to make. I'm a practicing litigation attorney with my eyes firmly set on retirement. I have a 26-year-old son. Like me, he inherited the gene mutation which can result in the development of transthyretin-related amyloidosis. My father died of heart failure from amyloidosis and spent the last few years of his life in a wheelchair due to polyneuropathy.

My family's gene mutation is known as cysteine 30 arginine. It causes amyloid deposition in both the nerves and heart. My neurological

symptoms date back to 2002 when I had bilateral carpal tunnel surgery. My cardiac symptoms started in 2007 with seemingly benign palpitations. By 2016, I was suffering with shortness of breath, arrhythmias, wheezing and the intractable cough, and worsening neurological symptoms. Specialists at UCSF and the Mayo Clinic diagnosed me as suffering from cardiomyopathy and polyneuropathy, both from amyloidosis.

I was advised in 2016 that due to the rapid progression of my heart failure and the lack of any approved treatment for TTR amyloidosis, I would probably only live another 3-to-5 years. Amyloid specialists recommended that I undergo a heart and liver transplant to prolong my life. I went through workups at UCSF to get on transplant lists while remaining in denial about a fatal diagnosis. While being pressed for a decision on transplant surgery, I stalled. You see, I had learned about new drugs in development, including patisiran. The promise of these new drugs kept me from agreeing to transplant surgeries.

In 2018, I began treatment with patisiran. My doctors wholeheartedly endorsed my decision. After three months of infusions, I could tell my symptoms were not getting worse for the first time in over two years. After one year of treatment with patisiran, biomarker blood tests confirmed that my heart failure had improved. I was no longer that guy who was constantly coughing, wheezing, and getting short of breath with ordinary activities.

I've had 77 infusions with patisiran, and am now on the second-generation drug, Amvuttra. I have learned that TTR amyloidosis is not just a neurological disease or a cardiac disease; it is systemic. Without having patisiran available to me, I would have succumbed to heart failure or the need to undergo transplant surgery with no favorable long-term prognosis. Instead, I have outlived a fatal prognosis. I hope that others with TTR cardiac amyloidosis are allowed to obtain treatment with patisiran. They, too, deserve that hope. Thank you for your time and kind

consideration.

DR. BUTLER: Thank you very much.

I think speaker 14 is unavailable, so we'll move to speaker 15. Please unmute yourself and your webcam, and state your name and organization you might be representing. You have 3 minutes.

Speaker 15?

DR. WOLINSKY: Thank you. My name is Dr. David Wolinsky, and I'm from Cleveland Clinic, Florida. I do have some conflicts I make, some from Alnylam, Pfizer, and BridgeBio, and a speaker for Alnylam and Pfizer. I'm a board certified cardiologist, and I'm director of the Cardiac Amyloid Center at Cleveland Clinic, Florida. This is the largest cardiac amyloid center in the Southeast U.S., and with my colleagues, we follow between 350 and 400 patients with cardiac amyloidosis. As such, I have vast experience treating both hereditary and wild-type ATTR cardiomyopathy.

These patients span the breadth of disease from barely symptomatic to class IV cardiogenic

shock. Tafamidis is the only approved treatment for ATTR-CM. With optimal multidisciplinary care, these patients often do well for long periods of time; however, it's been my experience that when a patient with cardiac amyloidosis deteriorates, their deterioration is often not from cardiac causes, but from systemic and neurologic deterioration. This deterioration can be associated with multiple hospitalizations and worsening quality of life for which the patients and their families have little support. At that point, there is little that standard of care can offer these patients.

Not infrequently, I see patients with mixed phenotype amyloidosis; that is patients with hereditary ATTR with both cardiac and neurologic symptomatology. In some of these patients, I have chosen patisiran as the disease-modifying therapy of choice. The neuromuscular and systemic symptoms improve. The patients gain weight, walk further, and experience greater overall functional capacity. In the meantime, we optimize their cardiac

management. Despite being so seriously ill on presentation, these patients often do quite well with good quality of life for 2-to-4 years. Their neurologic disease responds favorably, and their heart failure remains compensated.

However, we've just begun to scratch the surface in identifying patients with ATTR cardiomyopathy. There are approximately 750,000 cases of heart failure identified each year. Approximately half of these are patients with heart failure and preserved ejection infection. It's estimated that 10-to-15 percent of these patients have ATTR cardiomyopathy as the basis for their disease.

The literature suggests that a favorable clinical response to tafamidis is neither uniform nor predictable on an individual basis. Tafamidis is approved to stabilize, i.e., prevent progression of cardiac disease, in patients with ATTR cardiomyopathy. For many patients, the use of stabilizers is inadequate to provide a reasonable quality of life, let alone improve survival.

Based on the observations above, I believe clinicians should have access to tafamidis available as an alternative therapy for ATTR cardiomyopathy. I thank you for allowing me to present my opinion.

DR. BUTLER: Thank you very much.

May I request speaker 16 to please unmute and turn on your webcam? Introduce yourself, your name, and any organization you might be representing. You have 3 minutes.

MS. LOUSADA: Yes. Thank you. My name is Isabelle Lousada, and I'm founder and CEO of the Amyloidosis Research Consortium. I do actually have a couple of slides to share, so maybe those can get pulled up. ARC is a nonprofit dedicated to improving and extending the lives of those with amyloidosis. ARC is committed to collaborative efforts that accelerate the pace of discovery and improve short- and long-term outcomes in patients with amyloidosis.

The ATTR treatment landscape has improved drastically over the first five years; however, it

still remains that this multisystemic disease has a profound impact on physical function, activities of daily living, social and role functioning, and mental and emotional well-being. Earlier this year, we designed and launched a survey with the goal of reassessing the burden of ATTR in patients and caregivers in the setting of new therapies, and ultimately identifying what the unmet need is.

The study generated a unique set of patient-level data, including clinical characteristics; current and prior treatment history; impacts on health-related quality of life, as well as patient preferences; and personal goals and concerns of their treatment. Almost 400 ATTR patients participated, 315 of which reported having cardiomyopathy. Seventy-one percent of those patients reported that they were being treated with commercially available therapy; 22 percent were enrolled in an ATTR-CM therapeutic clinical trial; and only 3 percent reported not being on any treatment. Of those on treatment, almost half of the patients, 48 percent, reported that they did

not know or could not tell if their current treatment was impacting their disease.

We asked patients to rate the importance of nine different treatment factors in the context of their own personal treatment goals and concerns. This chart shows the percentage of ATTR-CM patients rating each factor, with red being of little to no importance, and with lighter to dark green showing more importance. This shows how overwhelmingly important slowing disease progression and extending length of life out to patients, whether a treatment improves symptoms or keeps them out of hospital, is also at least very important for the majority of patients.

We next tell patients to rank-order these same treatment factors, from 1 meaning most important to 9 meaning least important. This chart reiterates how consistently extending life and slowing progression are the most important factors to patients. The risk of common side effects, and even rare but serious complications that cause hospitalizations are important, but coupled with

the previous slide, these data suggest that, to patients, the potential risks of treatment are not as important as allowing them to live longer or slow the disease progression.

In the context of a rare disease, it's important to take into consideration patient perspectives. ATTR-CM patients currently only have a few treatment options, and many of those patients are uncertain whether or not that treatment is even impacting their disease. These patients continue to voice their overwhelming desire for additional treatment options that are able to delay their disease progression, and thereby maintain their quality of life. Thank you.

Clarifying Questions (continued)

DR. BUTLER: Thank you very much. I appreciate that.

This concludes the open hearing portion of this meeting, and we will no longer take comments from the audience. We have about 5-6 minutes still left in this session, so we can utilize this additional time for any remaining clarifying

questions that the panel members might have either for the FDA or the applicant. Also, the applicant, if they had the opportunity to look at the mechanistic data by tafamidis use, if they want to go over that data, we can utilize this time for that as well.

Please raise your hand if you have a question.

Yes?

MR. SLUGG: Sorry to interrupt, Dr. Butler, but we do have the data requested not only by Dr. Cella, but by Dr. Peterson as well, and we can quickly go through those for you.

DR. BUTLER: Please do.

MR. SLUGG: Thank you. Let me turn it over to my colleague, Dr. John Vest.

DR. VEST: John Vest, Alnylam. The first request was to see the distribution on the KCCQ response thresholds with the 5-point cutoff. We're showing that here. You can see that in patients who declined or died, the breakdown, 64 patients on patisiran, four of which were deaths, and

76 placebo, nine of which were deaths; 49 and 55 patients were stable, and 61 and 42 patients demonstrated an increase, respectively, of 5 points or more.

The next request was for KCCQ by greater levels of thresholds, by greater levels of change, and we're showing that here. We're putting both the increase by 5 points or decrease by 5 points, or changes of 10 points or more, in either directions. And again, we see the same thing; that the best outcomes are always more common on patisiran, and the worst outcomes are always more common in patients on placebo.

This raises a very important point, that in the progressive disease such as ATTR amyloidosis, benefit can occur in two ways, either by improving from baseline or by reducing decline. So remaining stable is a very good outcome in this disease, and this is a very important concept in interpreting the CDFs that were shown by the FDA and were included in our briefing document as well. These CDFs show exactly what's shown in the bar charts,

that no matter what your starting KCCQ is, patisiran treatment has better odds of benefit, either by improving or by having less progression.

We saw the same pattern with 6-minute walk test, as we demonstrated in the thresholds there, no matter what threshold we choose, the best outcomes are in patisiran and the worst outcomes are in placebo. And our corroborating data, New York Heart Association class in ATTR amyloidosis disease stage, again corroborates this concept of less progression with patisiran.

The biomarker data we shared, and we indicated after the break we would share that by baseline tafamidis, and we'll show that here. These are the biomarker results during the double-blind period in background tafamidis. We're showing NT-proBNP on the left and troponin I on the right. With NT-proBNP, there are wide confidence intervals, and there's o no indication of improvement with patisiran. With NT-proBNP, directionally patisiran is in the wrong direction, but with troponin I, we see the opposite picture,

that it looks a little bit better for patisiran. But again, the confidence intervals for both of these are very wide. For a comparison, we'll show here the monotherapy results, patisiran monotherapy, where again we see substantial and robust improvement with patisiran compared to placebo. So we are left, based on these biomarker data, again, with uncertainty with regard to any treatment effect with background tafamidis.

If it would be allowable to the chairman to help address the previous question from Dr. Roy-Chaudhury about clinicians' perspective on these issues of use case, we would like to have Dr. Drachman, who has treated over 40 patients with the combination of patisiran and tafamidis on our EAP, comment further, if that would be allowed.

DR. BUTLER: We are right at the top of the time, so please just try to limit to 60 seconds.

DR. VEST: Thank you.

DR. DRACHMAN: Hi. I'm Brian Drachman. I'm the founder and co-director of the amyloidosis program at the University of Pennsylvania Health

System, and have treated, myself, over 850 patients in the last 5-to-7 years with various types of amyloid. Our program has treated in the thousands.

One of the things that's been brought up a number of times is that this is a disease that progresses with time, and I've been, for example, taking care of patients on tafamidis for over 10 years because I was part of the ATTR-ACT trial, and I will tell you that despite being on tafamidis, these people get worse, and they die. There is no question about that. I'm not saying it's not an effective drug, but it is clearly not a cure for this disease.

Although we do not have data that firmly says that the effect of patisiran would be additive to tafamidis, it's already been discussed that mechanistically, it totally makes sense why it would be. Tafamidis is a stabilizer, but we know that it does not stabilize close to 100 percent of the TTR tetramers. There's variation from patient to patient and mutation to mutation, so adding a drug that basically will suppress over 85 percent

of the precursor protein should only benefit what's happening with tafamidis.

I will tell you that I tend to add it fairly early in patients, in the appropriate patients, not in every patient. The reason being, that it's already been shown in the open-label extension, both in APOLLO-B, as well as the open-label extension in the ATTR-ACT trial, that waiting for patients to deteriorate gives them irreversible damage that will never be recovered.

So my bias at this juncture is we have a drug that, I believe, based on the data out there, does improve outcomes. Can I prove that it's additive to tafamidis? No. Have I seen many, many people deteriorate on tafamidis? Absolutely. I think this is an important option that we should have available for our patients.

DR. BUTLER: Thank you very much.

I see a hand raised by the FDA. Is there a comment that the FDA would like to make?

DR. SENATORE: Yes. Thank you very much. Our colleagues from DCOA and PFFS groups would like

to make a comment, so I'd like to call on Dr. Illoh first, and then later, Dr. Morell, to make comments.

DR. ILLOH: Hi, everyone. This is Onyekachukwu Illoh, team lead in the Division of Clinical Outcome Assessment. Thanks everyone, for your time at this meeting. I wanted to add to the discussion, and I would like you to know that in the absence of the patient's voice on what is considered a meaningful change in the APOLLO-B trial, and as an exercise of regulatory flexibility, FDA attempted to utilize data from the APOLLO-B trial to interpret the results of the 6-minute walk test.

So specifically, we asked the applicant to conduct a post hoc, anchor-based analysis using the KCCQ item 1.3, which asks patients how much they were limited in their ability to walk one block on level ground to support the interpretation of meaningful change in the 6-minute walk test. We chose this item as it appeared to align closely with the measurement concept of the 6-minute walk

test; however, there was limitation with this approach, as the inclusion criteria for the APOLLO-B study selected patients who would likely have no difficulty in walking one block on level ground, and we did observe poor correlation between the change scores for item 1.3 and the 6-minute walk test. So hence, the KCCQ item 1.3 didn't turn out to be a good anchor.

Also, while the applicant had proposed two alternative anchor approaches based on the KCCQ Overall Summary Score and the Physical Limitation Score, you have previously heard from Dr. Pretko that the OSS and PLS, for short, are not anchors, so specifically, the measurement concept of the OSS and the PLS do not necessarily align with that of the 6-minute walk test, and the OSS and PLS require their own interpretation.

So ideally, administering appropriate anchor scales in the APOLLO trial would have been useful for deriving a range of meaningful change thresholds for the 6-minute walk test and the KCCQ Overall Summary Score, and by appropriate anchor

scales, I mean anchors which are associated with the target COA endpoint in a way that addresses the question of clinical meaningfulness of that target COA endpoint; also, anchors which are easier to interpret than the COA itself; and anchors whose recall period are consistent with the assessment period of the target COA endpoints to the extent possible; and in addition, supplementing the anchor-based data with qualitative patient inputs on what patients consider to be a meaningful change from baseline and whether or not they believe the experience of meaningful change during the trial would have been informative.

So as such, we conclude that there is lack of information to support the interpretability of clinical meaningfulness of the statistical result of the APOLLO-B trial, and the applicant was limited in the ability to provide such supportive evidence.

I would also like to turn it over to Dr. Morell to provide further comments. Thank you.

DR. BUTLER: Thank you.

DR. MORELL: Thank you. This is Dr. Monica Morell, psychometrician and statistical reviewer for CDER. We reiterate that including patient voice is critical in how FDA evaluates clinical meaningfulness in COA-based endpoints. As there were no appropriate anchor measures administered, nor qualitative data collected in APOLLO-B, we conducted an extensive literature review on the KCCQ, and found many limitations with the anchor-based methodology used in the literature, for example, using a 15-point anchor measure and arbitrarily grouping the responses into 7 categories; the reliance on small improvements to derive what is considered meaningful to patients without evidence; and the lack of any assessment of the impact of baseline symptoms severity on the estimates of meaningful change.

Such limitations make it so that we cannot generalize the findings in the literature to the current trial and are unable to conclude that a 5-point change represents a clinically meaningful change to patients on the KCCQ-OSS. That is to

say, based on our current assessment of the application and of the literature, a 5-point threshold is inappropriate, both to interpret the key secondary KCCQ endpoint and to interpret the primary 6-minute walk test endpoint.

I would also add that based on our extensive experience reviewing multiple applications and multiple indications, patients' views on the degree of change that represents a clinically meaningful improvement or meaningful deterioration is generally not symmetrical. The amount of change that is considered a meaningful improvement is generally not the same amount of change that is considered a meaningful worsening. To apply a single number as a threshold for meaningful change, regardless of the patient population or patient baseline status to both improvement and deterioration, is very unusual and would need evidence to support this claim. Thank you.

DR. BUTLER: Well, thank you very much.

So because we are running a little bit behind, my apologies to the panel members who have

their hands raised, but I will probably conclude this session at this point, and move on to the next section. In order for us to have a panel discussion, I will request Dr. Norman Stockbridge to proceed with the charge to the committee.

Charge to the Committee - Norman Stockbridge

DR. STOCKBRIDGE: Yes. I think we've had a very good discussion up to this point, and I don't have anything at all to add as context. I think we're ready to go into the questions that you have.

Questions to the Committee and Discussion

DR. BUTLER: Thank you very much, Dr. Stockbridge.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observations, public attendees may not participate, except at the specific request of the panel.

After I read each question, we will pause for any questions or comments concerning the wording, and in the absence of any further concerns, we will proceed with a discussion.

A couple of quick reminders and requests to the panel members; one, we have five discussion questions and one voting question, and we have a little over an hour to go over this discussion. Necessarily, some of the discussion points overlap; however, the more we can limit our discussion to the discussion question that we are discussing, I will very much appreciate it, and not jump; for instance, there is a tafamidis interaction question further down, and if we can limit those questions when we are discussing that discussion as opposed to mixing these various different observations.

Second, I would definitely appreciate a robust discussion from all members, including voting and non-voting members. But finally, please remember that in this section, we will be having a discussion, but please do not disclose which way you're leaning in terms of which vote you think

this should be. We will have an opportunity at the end, after the voting, to discuss what our perspectives are. This section is about discussion.

This is the discussion question, or question 1 for discussion. Discuss the magnitude and clinical meaningfulness of patisiran's treatment effect on 6-minute walk test.

Is there anything regarding the wording of the question that we need to discuss, or is it pretty clear to everyone?

(No response.)

DR. BUTLER: Hearing none, none of the questions regarding the wording, we will now open this for discussion.

(No response.)

DR. BUTLER: Any panel member may want to start, and if not, then maybe I can start the discussion by posing a question. There was a robust discussion and a distinct different perspective by the applicant and the FDA, whether using KCCQ as an anchor to decide the minimally

clinically important difference in 6-minute walk test was an appropriate way of assessing MCID for 6-minute walk test.

DR. CELLA: Dr. Butler, this is David Cella. I have my hand up, so I'm just wondering, during this session, are you not asking us to raise our hand? You would rather we just speak?

DR. BUTLER: I would appreciate if you'd raise your hand so that I can understand. I did not see your hand raised, but maybe I missed it.

DR. CELLA: It was just lowered by the system or it's going down by the system.

DR. BUTLER: Okay. So if we can use the same method that we've been using all along, to raise the hand, and that gives me a cue who to go to next.

DR. CELLA: Maybe I raised it a little late, but I can start if you like.

DR. BUTLER: That will be great. Please do.

DR. CELLA: Well, it's been a very fascinating day. I've learned a lot about this clinical area, it not being an area that I'm well

versed in, but I'm pretty well versed in the 6-minute walk and the KCCQ, so happy to speak on those topics and hear from others on the other topics.

This is a small number. I think that's a big part of why we're here. We have a primary endpoint met with a very small number. I'm pretty familiar with the literature, and there's a general consensus around 25-to-30 meters as being toward the low end of what's a clinically meaningful -- I don't know about clinically meaningful necessarily, but with a significant difference that is meaningful, or tends to be. That number drops down below 30 in some studies, but I think just comparing this number to the literature, it's quite small. It's a large sample, so it's statistically significant, but I think it is small, and I think that's a big part of why we're having this meeting.

As to your question about the appropriateness of the KCCQ as an anchor, I would zero in on the low correlations that the KCCQ and the anchor have, but the FDA preferred to focus on

the content relevance and appropriateness, and that's reasonable. Also, the correlations were on the low end, and the lower you go with correlations of an anchor, the smaller -- this is kind of one of these paradoxes. The lower the correlation of an anchor to the test you're interested in -- the lower it goes -- the smaller the estimated MID becomes, which is one of the reasons, just in this field, I'm not a big fan of the M in MID. So I would say that's one significant concern about the use of the KCCQ as an anchor, which probably does need to be understood.

DR. BUTLER: Thank you.

Dr. Bairey Merz?

DR. BAIREY MERZ: Thank you, Dr. Butler. I would completely agree with David, and I would just add, listening to the patient testimonies, it's very clear to me that possibly the 6-minute walk test was not appropriate for this ambulatory population, who probably had a lower prevalence of the peripheral neuropathy. I would be even more concerned about that because of the overlap of

symptoms. Fatigue is fatigue, muscle weakness is muscle weakness, and it's going to be hard to know if it's coming from the heart or the peripheral neuropathy. In the prior study with the robust improvement in walking time, potentially, as Dr. Peterson was bringing out, they may not have just had a sick enough disease to see it in this APOLLO-B.

So I found the patient testimony very enlightening, and I would suggest to the sponsor to consider analyzing that more carefully with grades of severity of the neuropathy. It did not look like it was an exclusion criteria. Thank you.

DR. BUTLER: Great. Thank you very much.

Dr. Moliterno, your hand was up, and I just was making sure it did not inadvertently go down.

DR. MOLITERNO: Thanks, Dr. Butler. No, I think Dr. Bairey Merz covered what I was going to say. I think we all see a benefit. The question is, as David said in the beginning with some magnitude and clinical meaningfulness of it, there's a small benefit. We see that. But

relative to the patients' current functional capacity, it's relatively small, a 4 or 5 percent impact on the 6-minute walk test, and is that meaningful enough.

We'll get to it later, but it's all relative to, I guess, potential harm, potential cost, potential convenience or inconvenience of receiving the drug and, fortunately, it's a relatively safe drug, but I won't jump to that for now, so no other comments. Thank you.

DR. BUTLER: Thank you. I mean, personally, from my perspective, whether the magnitude of benefit was meaningful is something that we can all have our perspective, but using KCCQ as an anchor to determine that, while there may not be a lot of precedence for that, at least the rationale that was given was reasonably meaningful to me and, of course, should be replicated in future studies as well. And maybe it's not what we have done commonly before, but I was actually reasonably convinced by the rationale that was given.

Any further comments related to the

magnitude of clinical meaningfulness of patisiran treatment?

(No response.)

DR. BUTLER: Hearing none -- please go ahead.

DR. ROY-CHAUDHURY: Let me raise my hand. Sorry. Again, really, I learned a lot from all of these discussions. I just want to put out that the durability of the effect was something that keeps coming back to me over a prolonged period of time, which obviously if the data that was shown is correct, would mean that the overall ultimate impact of that 6-minute walk test over time would actually be quite beneficial. I understand completely that the study was a 12-month study, and that as we look to the open-label study, obviously that's not as clean. But I just wanted to make that point.

DR. BUTLER: I think we did see somewhat of a modest benefit in the first 6 months, and that expanded over time, but that may be consistent with the fact that it may take some time for the

medication to act and lower the burden of amyloid. Great.

DR. ROY-CHAUDHURY: Thank you. That's the end.

DR. BUTLER: Thank you.

Any other comment from any panel members on this question?

DR. THADHANI: Butler, I think Dr. Abernathy and myself have our hands up.

DR. BUTLER: You know, I need to -- okay. Yes.

Please, Ms. Abernathy?

MS. ABERNATHY: Thank you. As a hereditary amyloidosis patient, I was a mixed phenotype. I think one of the frustrations from my perspective, as well as other patients I know, has been that the disease has often been categorized as either cardiac or affecting neuropathy. It's difficult to imagine, as was stated a little bit earlier, that the 6-minute walk test might not also be affected by the degree of progression of the neuropathy, and I know that it happens differently in different

patients.

For instance, my father, who died at 49 from this disease in 1968, was bedbound for 4 years with severe polyneuropathy, yet I had cardiomyopathy for a good 10 years before I was diagnosed, and only developed polyneuropathy, progressively of course, after having had a heart and a liver transplant in 2012, despite having been suspected of having amyloidosis many, many years prior to that. So the 6-minute walk test just does not seem, to me, to be a very clean, if you will, way of measuring progression. Thank you.

DR. BUTLER: Thank you very much.

Dr. Thadhani?

DR. THADHANI: Thank you, Dr. Butler. Ravi Thadhani. I was struck by the conversation from the agency on the precedence of using these functional measures as endpoints in clinical trials, and the precedence going into this study that very few studies, at least in this arena, have necessarily received the registrational approval using functional measures, and more importantly the

lack of a cut-point that we can all then converge on and necessarily celebrate and say, if they met it, wonderful, and if they didn't, they would not.

What that necessarily does to myself, at least, among the members of this panel, then, is it forces us to look more critically at the aggregate data, the totality of the data, and the threshold less important, but the totality with regards to other measures, and the consistency. This is just a comment, Dr. Butler, but we're then left necessarily with looking at everything else, not the least of which includes risk, which I know we'll come to, so thank you.

DR. BUTLER: Thank you very much.

Is there any other panel member that has a comment to make before I summarize the session? Because on my display, sometimes it's jumping who has their hand up.

(No response.)

Hearing none, let me just quickly summarize what I thought I heard, and if I'm missing something, if somebody wants to add to that. There

are varying opinions to the magnitude of the benefit that was seen and whether that was clinically meaningful or not, and similarly, there were some varying opinions in terms of how the MCID was calculated and whether KCCQ is an appropriate anchor to be doing that evaluation or not.

There were some comments also made in terms of the benefit was limited to 12 months and that perhaps there are reasons to believe that over time, more benefits might accrue as well. There were also comments made that having a single standard across the entire spectrum of disease and across various diseases is perhaps not appropriate and whether patients at different levels of sickness may have different benefit, and whether that should be accounted for as well. And similarly in the same light, another comment that was made is that looking at the overall literature on 6-minute walk test and the variations in what is considered a threshold for improvement, perhaps rather than pinning yourself to one specific number, maybe the decision ought to be made on the

basis of totality of evidence both for benefit and for risk. These were varying opinions for the committee members.

Does anybody want to add to the summary I presented? Otherwise, we'll move on to question number 2.

(No response.)

DR. BUTLER: Hearing none, may we move on to question 2, please?

Question number 2 states, discuss the magnitude and clinical meaningfulness of patisiran's treatment effect on the Kansas City Cardiomyopathy Questionnaire Overall Summary Score. Before we begin the discussion, are there any comments or issues related to the wording of this question?

(No response.)

DR. BUTLER: Hearing none, we will open this up for discussion. So again, let me take the prerogative and start this discussion.

Linking the KCCQ back to the 6-minute walk test, again, the magnitude of benefit is something

that we all have our opinions on, but in terms of using the KCCQ anchor, the primary anchor that was used was overall summary score, which was similar to the primary endpoint, so it does make sense, although overall summary score comprises a lot of different domains.

What is more pertinent to activity level perhaps is the the PLS, physical limitation score, and the sensitivity analysis was pretty consistent with what we saw with the overall summary score, so that was helpful. But in terms of the overall summary score and the benefit that we have seen, about 3.7, and whether to use a fixed anchor of 5 as clinically meaningful from previous studies is something that we can discuss.

Maybe I can invite Dr. Cella to make some comments.

DR. CELLA: Thank you. Well, I think, just like the first question and just like the primary endpoint, this is a very small difference, group difference, based upon other studies in the literature and what we know about the KCCQ. In

effect size terms, the effect size of the difference is 0.18, which is less than the conventional 0.2 that one wants to see for a small effect. Incidentally, for the 6-minute walk, it's 0.14, so even slightly lower than the 0.18.

Perhaps more importantly, and part of why I asked about the 10-point difference, there's a concern about using group-based information, particularly with relatively low correlations, and I'm talking now about prior literature that established the 5-point difference. Using group-based information to then say that should be used to classify individuals as change is problematic because of error. I mean, the error in one person's score is much greater than the error in a group average score.

We usually like to see that be increased, and that's why I asked about 10 points. Looking at the 10-point information, there's still an advantage. We saw that in the cumulative distribution function as well. So there is still an advantage. It's like a light wind blowing in

favor of patisiran over placebo, but it's a very small advantage that needs to be weighed later with all the other evidence.

I just would add one other thing, which is we didn't talk about number needed to treat. I didn't necessarily recall exactly what those differences in percentage were for the 10-point difference, which I would regard as a reasonable score change to classify somebody as changed, whether for the worse or better, but I think they were a little south of 10 percent on each side, which would be a number needed to treat of around maybe in the 10-to-12 patient arena, and that might be worth considering to the cardiologist and to the patient community. Would a 1 in 10 or 1 in 12 chance of getting a benefit be worth it? I just put that out there if you buy into the 10-point number, so thank you.

DR. BUTLER: Great. Thank you very much.

Dr. Bairey Merz?

DR. BAIREY MERZ: Yes. Dr. Cella said what I was going to say, so I lowered my hand, but thank

you.

DR. BUTLER: Dr. Peterson?

DR. PETERSON: Yes. I don't have much more to add than what Dr. Cella added. I very much like the first discussion. The positive notes are that the results are pretty darn consistent any way they cut the data among subgroups. It follows a nice predictive curve, getting more over time. Unfortunately, the measured difference at the end of the study was small right at that border, and even less than the border we typically think of as clinically meaningful, based on prior studies and comparison of literature. That's where we sit.

The data post-randomization, or when we get to the open label, on the one hand, it's positive. It looks really good. The curves, particularly for the control group, go up, which would be seemingly showing an effect of the drug, but we don't know there if patients have a placebo effect, which could conceivably be affecting what's happening. They know they're on therapy now, so any kind of shift that happens after that to me is

uninterpretable, unfortunately, given the data that we have so far.

So it's tough. It would have been ideal if the study would have been run longer to see if these curves continue to diverge while blinded to the therapy that was given, or that we would have seen the effect that they had postulated at the beginning of the study in terms of a magnitude of difference that would have made it more unambiguous than we are now. That's all.

DR. BUTLER: Dr. Moliterno?

DR. MOLITERNO: Yes. Thanks, Dr. Butler. David Moliterno. I don't have a lot more to add to the others. I have a minor background concern mainly because I don't know the tafamidis data well, but noting that the non-Caucasians reported here, the roughly one-fourth of patients who showed no benefit or neutrality, if you will, if we say there's a small benefit in the KCCQ, it looks to be even less than that in the non-Caucasians. So again, I appreciate it's a subgroup, and it's really quite small, but just throwing that comment

out there that either looking back at the tafamidis data or urging the sponsor to get more data in African -- or blacks, and other non-Caucasian groups. That's all. Thank you.

DR. BUTLER: Well, thank you very much.

I mean, I think the challenge that we have is the precedence and what difference in population-based KCCQ is clinically meaningful. If you actually look at 3.7 numerically, this is higher than most of the heart failure therapies that we have seen, except that they were not seeking regulatory approval for KCCQ or for health status improvement. But for most of the therapies, it has ranged somewhere between 2-to-3 population-based differences, and that's where this issue of responder analysis comes in.

Again, we can argue whether a 5-point improvement in this particular disease's data and in this particular patient population is appropriate or not, but the overall literature, in the heart failure world at least, would suggest that various different diseases -- HfrEF, HFpEF,

iron deficiency -- it sort of pans out that it's somewhere in that neighborhood. But I think our challenge here is that the 3.7 is not comparing with other therapies, which we know are comparable, but whether this is significant enough, clinically meaningful enough, for approval per se.

Dr. O'Connor?

DR. O'CONNOR. Yes. I just want to jump in and say that I think we're all in agreement that the magnitude feels small and low, but in my opinion, the clinical meaningfulness is unclear, as you highlighted nicely. And in this specific disease state, maybe these small numbers in this elderly population, in this disease state, maybe it is meaningful. We just don't know.

When we ran HF-ACTION study, exercise training in 2000 HFrEF patients, the KCCQ change and the 6-minute walk change are identical to what we see here, and those translated into a significant reduction at 2 years in heart failure hospitalization. So I think, as Eric pointed out, there were significant design flaws in this study.

I'm sad by that because I think these could have been avoided, and that duration is one of them, but I think there are many of them.

I think the endpoint choice could have been a win ratio with clinical and functional components to a composite endpoint, and I didn't hear whether adaptive monitoring was used to understand that they were -- as the trial was going on, they weren't meeting it even in an aggregate look, the type of changes that had been postulated at the beginning of the trial. So I would say for both one and two, magnitude small and meaningfulness unknown in this disease state.

DR. BUTLER: Thank you, Dr. O'Connor.

Any other comments before I summarize this discussion?

(No response.)

DR. BUTLER: Hearing none, this discussion pretty much reflected what we discussed with the 6-minute walk test and very well summarized by Dr. O'Connor at the end that there are some design-related issues, which makes the

interpretability of these results a little bit difficult. The numerical differences are modest. The clinical meaningfulness is a little bit difficult to ascertain. The numerical differences are pretty consistent with some of the other disease states where KCCQ has been measured.

There was no MCID for KCCQ with anchor-based analysis using something like PGIS/PGIC done in this particular study that we saw, but the responder analysis with 5 points and 10 points was positive, and there were comments made that if you are positive in responder analysis with a 10-point improvement, then you can get a little bit more comfort that the results are clinically meaningful.

Is there any other comment anybody wants to make about question 2 before we move on to question 3?

(No response.)

DR. BUTLER: Hearing none, can we move on to question 3, please? I will again read the stem. Discuss whether patisiran has other established clinical benefits for the treatment of

transthyretin amyloidosis, ATTR, cardiomyopathy?

Does anybody have any issues with the wording of the stem?

(No response.)

DR. BUTLER: Hearing none, we will open this up for discussion. So again, I will take the liberty of starting the discussion.

The magnitude of benefit in APOLLO versus APOLLO-B does raise concern of why was the benefit attenuated, but then sometimes we really get into the nitty-gritty subgroup analysis, and if anything, we would have seen attenuation of benefit with the tafamidis group, but it was people who were not on tafamidis that tended to have no mortality benefit, which warns us against looking too much into subgroup analysis, and may have some random results that we then have to contend with.

Dr. O'Connor?

DR. O'CONNOR: Yes. I think you've said it well. I think the clinical benefits are unknown, unfortunately, because we didn't have a trial conducted that had sufficient number of clinical

events. There are, however, I think a number of important signals that line up in this entire data set of the two trials, and that is imaging structure looks favorable. I'm very impressed with the delta in the NT-proBNP, and as you know, we're getting close with that marker. It's getting close to being a validated surrogate. It's not now, but it's an important biomarker that we base a lot of our phase 2 decisions on in clinical trials, so that was an impressive delta, I think.

Then you've got the functional, the PRO, and then you've got the trend in all these post hoc analyses, whether it's the win ratio or whether it's the pooled analysis of hospitalization and death that looks favorable without statistical significance, so lots of lining up, but it's still clinical benefits unknown.

DR. BUTLER: Thank you, Dr. O'Connor.

Dr. Moliterno?

DR. MOLITERNO: I echo what Dr. O'Connor said, that you've got this nice biologic underpinning that does lead to serologic changes

that maybe aren't directly clinically beneficial, but they have been found to be directly beneficial in other studies, and obviously in our own clinical day-to-day practice. And then I guess there's an indirect benefit, not to sound snarky but just having to present to a healthcare provider every 3 weeks. There's probably some benefit to that, too, even though it's obviously not directly related to the drug; it's just a requirement for the drug to be infused. That's all. Thank you.

DR. BUTLER: Thank you very much.

Any other comments from the panel members?

(No response.)

DR. BUTLER: I think this section was pretty straightforward that it is difficult to make any conclusive comments on the clinical endpoints, considering the small number of events. But the totality of evidence, looking at a biomarker and remodeling data, does give hope in the right direction, but we do not necessarily have the numbers to make any definitive conclusion, and that was not the primary endpoint of the trial itself.

Dr. Roy-Chaudhury?

DR. ROY-CHAUDHURY: I was just wondering whether you're going to extend the question on to the second part and also discuss whether there is a patient population that would benefit from patisiran monotherapy. It was a long additional section. I mean, I can just jump into it, if you want.

DR. BUTLER: Please.

DR. ROY-CHAUDHURY: I did think that the comments that were made about the polyneuropathy and the cardiomyopathy being one disease were actually quite useful and important, particularly at a clinical-level physician and patient. So if you had a patient who had a lot of polyneuropathy and they had the cardiomyopathy, then patisiran would seem to be a really good drug to start off with, and that was the only comment I wanted to make. Thank you.

DR. BUTLER: Great comment. Thank you.

Any other comments on this section?

(No response.)

DR. BUTLER: Okay. Hearing none, can we move on to question 4? I will read the stem. Discuss whether there is clinically meaningful benefit of patisiran in patients with ATTR cardiomyopathy who are also receiving tafamidis. Also discuss whether there is a patient population that would benefit from patisiran monotherapy without tafamidis, taking into account that tafamidis is approved for reducing cardiovascular mortality and cardiovascular-related hospitalization in ATTR cardiomyopathy.

Is there anything regarding the stem which is unclear in terms of its wording?

(No response.)

DR. BUTLER: Hearing none, we will open it up for discussion.

Dr. Roy-Chaudhury?

DR. ROY-CHAUDHURY: I apologize. I got my numbers mixed up, so my apologies.

DR. BUTLER: No problem. No problem. I wasn't going to call you out. No problem.

Dr. O'Connor?

(No response.)

DR. BUTLER: You're muted.

DR. O'CONNOR: I think this is a really important question because, in my view, a lot of things happened here. There was capping of tafamidis, which I'm not sure why that was because what we saw in the open enrollment, we saw a large amount of tafamidis being used. I think that's what I saw from the FDA presentation, that a large number of patients were now on it. And it's first line, so, to me, it would be like doing a HFpEF trial today and capping SGLT2 inhibitors. It just doesn't make sense.

But having said that, we see an attenuated effect in those on baseline tafamidis, and the NT-proBNP was flat, and that was very worrisome to me. I think there is a swim lane. There's a greater magnitude of benefit in the tafamidis naïve patients. It's a small group. I don't know who that group would be because the inclusion criteria looked similar to me, but it may be cost or drug intolerance. Thank you.

DR. BUTLER: Thank you.

Dr. Thadhani?

DR. THADHANI: Thank you. Ravi Thadhani. The discussion I was struck by had to do with the potential evidence or was there any evidence of a combination effect, added effect, synergistic effect, of the two agents, I think going to the first sentence here. Biochemically, just given the complete knockdown, it was difficult to tell, at least through TTR levels, that there would have been potentially an additive or synergistic effect.

Clinically, I don't believe we saw -- at least I didn't recall any data that we saw from the sponsor that there would be an additive or a synergistic effect. If anything, I think we saw subgroup analyses that individuals who are also on tafamidis actually had limited, if any benefit. I think the forest plots demonstrated necessarily the point estimates of zero or very near zero -- or 1. I apologize. Thank you.

DR. BUTLER: Thank you.

Dr. Bairey Merz?

DR. BAIREY MERZ: I would just add, there might be a third lane, and to Dr. O'Connor's comments, encourage the sponsor to look at grading the polyneuropathy, understanding potential interactions, even tafamidis naïve patients. But those that are already on it, if they have severe polyneuropathy, there may be a window to be looking at for a third lane. Thank you.

DR. BUTLER: Thank you.

Dr. Moliterno?

DR. MOLITERNO: Thanks, Dr. Butler. David Moliterno. I struggled throughout the presentation trying to understand if there would be, in fact, a group that patisiran monotherapy would benefit, and I struggled. I mean, we just went through the challenge of finding benefit, and now trying to augment that by patients who could not take tafamidis. And again, I don't know the literature so well, but I don't know of there being any absolute contraindication to tafamidis, and my recollection from the early studies is that there was a very small, 1 percent or so, dropout rate

from drug intolerance or having to change the dose.

So I think it will be a struggle, and I'm hopeful that tafamidis won't be unseated, at least with the data so far, as a first-line therapy because I do think it's important. Thank you.

DR. BUTLER: Thank you very much.

So usually this section is a panel member discussion. I do see a hand raised by the applicant, so we'll allow a quick comment, if they have. Please go ahead.

MR. SLUGG: Yes. Thank you very much for the opportunity. We just wanted to help the discussion by making a few points of clarification. We heard a few times regarding the potential interaction between polyneuropathy and the primary endpoint. We have done analyses to evaluate this, and we're happy to share those. We found that there is no impact -- and there are very few patients with baseline polyneuropathy and no impact, and we can walk you through those data.

Also, there may be a misperception. The FDA mentioned a large number of baseline tafamidis

patients; it's in a totally separate expanded access protocol. There were very, very few patients who had tafamidis drop-in. There were less than 7.5 percent patients on placebo overall and 4.4 percent on patisiran in the entire 24-month period who had drop-in, so we just wanted to clarify that.

Also, to help and aid the discussion, at this particular point, tafamidis is not approved for polyneuropathy of this disease; patisiran is. We were happy to share the data on the polyneuropathy impact since many of the panel members did seem to have that aspect of curiosity during the discussion, on discussion item number 1.

DR. BUTLER: I think your comments have been very, very helpful, so I think that makes the point. Thank you very much.

MR. SLUGG: Thank you.

DR. BUTLER: Dr. Moliterno, your hand is still up. I don't know whether it's a legacy hand or do you have another comment. Okay.

One comment that I was really struck with,

and multiple experts mentioned this, is that people continue to progress on tafamidis, and having an alternate option would be very helpful. The problem is that this trial enrolled patients primarily NYHA II, and those patients who we might think are tafamidis non-responders and are progressing are probably going to have NYHA class III more often, and that's where we saw a negative interaction and not seeing the benefit in 6-minute walk test.

I don't know whether that's a real signal or not, but that makes the interpretation a little bit difficult to say that the non-responders are definitely going to respond to patisiran therapy, or are the non-responders so sick that they're not going to be responding because we did not see an NYHA III benefit as well. So that is something that I struggle with.

Dr. O'Connor?

DR. O'CONNOR: I think that's a really good point, and I struggled with those commentaries who came from multiple sources to say that this could

be used for patients failing tafamidis when the curves, the clinical curves for tafamidis, separate late. So you actually may be sliding down a little bit with disease progression, but those clinical effect curves separated at 24 to 36 months. And plus, this study did not address tafamidis failure, so I think that was a very misleading set of comments.

DR. BUTLER: Thank you, Dr. O'Connor.

Any other comments on the tafamidis interaction or the patient population?

(No response.)

DR. BUTLER: Hearing none, let me try to summarize what I heard. So I think there was pretty much a unanimous agreement that tafamidis interaction was of concern. How to interpret that from a clinical perspective is something that the panel seems to be struggling with. There are certain patient populations, for instance, those with polyneuropathy; those where there may be a cost differential; those where they may be intolerance to tafamidis, where patisiran may be

used as a first-line agent, but the trial was not necessarily designed particularly to answer those questions.

While there are patients who are progressing on tafamidis, this should be given as a second agent because in this particular interaction analysis that we saw, it was for all patients on tafamidis, not necessarily those who were progressing. But some of the data, especially with the NYHA III interaction, makes it difficult to interpret whether that patient population will be responsive to tafamidis or not.

Then there was just a general concern that the three potential uses as initial therapy, as rescue therapy, or as an add-on therapy, none of those were really either designed to be answered, or meaningfully answered per se, in this particular study, and that the benefit with tafamidis may take some time before it is evident, and how to even call the non-responder may not be that simple.

Is there any other comment related to four or anything that I missed in the summary

discussion?

Ms. Abernathy?

MS. ABERNATHY: Thank you. I'm not really sure where this comment belongs, but your discussion, or your mention of the fact that maybe some people cannot take the tafamidis, I think as Muriel Finkel pointed out in the public comments, there is a very real issue with access to medication and affordability, and I know that many of us have run into that, inability to get the medication that is recommended for us because of lack of realistic insurance coverage or people on Medicare not perhaps being able to access co-pay funding. So while that is not a clinical issue per se, I think it's a very real patient issue.

I could imagine that there might be cases, probably many, of people for whom tafamidis would be an appropriate medication but yet they would not be able to obtain it. All of these medications are extremely expensive, as we all know, so having an alternative might be appropriate and might be helpful. I just wanted to put that in. Thank you.

DR. BUTLER: Great comment. No right time for that really important comment. Thank you very much.

Any other comment or questions related to this topic or any of the previous three topics before we move on to question number 5?

Ms. Abernathy, your hand is still up. I assume it's from the previous one, and you don't have any -- great. Thank you.

Any other comment from anyone?

(No response.)

DR. BUTLER: Great. Hearing none, can we move on to question number 5? I will read the stem. Discuss whether patisiran has safety issues of concern for the treatment of ATTR cardiomyopathy.

Are there any issues that are related to the wording of this question?

(No response.)

DR. BUTLER: Hearing none, I will open it up for discussion.

(No response.)

DR. BUTLER: Any safety concerns related to the therapy?

Dr. Moliterno, you were mentioning something in the first comment related to safety. Please.

DR. MOLITERNO: Yes. Thanks. I think the good news in this story is while there may be small benefit, it doesn't look like there's a signal for harm, short of maybe some of the eye findings, which didn't bother me a lot. Again, somewhat tangential, my big safety concern is more secondary, that if some people do believe this is a viable alternative to a class I drug that's been shown to reduce mortality by 30 percent, I'd be concerned if, for whatever reason, tafamidis gets put on the side shelf when it's got established benefits; so not a direct safety concern, but an indirect safety concern. Thank you.

DR. BUTLER: Great. Thank you very much.

Are there any other comments related to safety?

(No response.)

DR. BUTLER: And because the next question

is actually a voting question, I would also invite all panel members, if there is any final question that they might have for the FDA or the applicant, maybe we will make an exception and take a couple of quick questions, if need be, because there were a couple of questions that I did not allow because of time considerations, or any comments related to the first four questions as well.

Dr. Cella?

DR. CELLA: Yes. Thank you. This is a question for the FDA. I realize that the vote we're being asked to make is whether the benefits outweigh the risks, so you're not asking us to vote on whether we think the drug should be approved. But my question is about approval options that you have, and I ask that because we have the data in front of us, and we have a statistically significant primary endpoint that was hit by the trial, very small, potentially not meaningful clinical benefit, associated with the two endpoints we've discussed, a minimal safety signal. But from the public comments, as well as the sponsor, and

even some of the panelists, we've heard this idea that getting access to the use of this drug in patients would be of value, particularly, for example, in tafamidis failures, and yet there aren't data on treatment of tafamidis failures.

So is there an approval option that you have that allows something to move forward, but provisionally, in this particular context, conditional on further research? That's my question. I hope that was clear.

DR. STOCKBRIDGE: Yes, I think it is clear. The only pathways to approval in the United States are regular approval, which was what we were contemplating here, and accelerated approval, where there's a reasonably likely surrogate endpoint and a study that somebody's prepared to do to resolve the actual clinical benefit, but we've not discussed a basis for an accelerated approval. But in the United States, there is no conditional approval.

DR. BUTLER: Thank you, Dr. Stockbridge.

Dr. O'Connor?

DR. O'CONNOR: This is just a question to the sponsor, real quickly. As you look at the totality of data that we've seen today, is there any reflection that we may not have been at the top of the dose-response curve, and could that be an explanation for the attenuated small efficacy changes?

MR. SLUGG: Let me have my colleague, Dr. Robbie, address your question.

DR. ROBBIE: Yes. Gabriel Robbie, Alnylam. So we are at the top of the dose-response curve, and we know this because we have done clinical trials, and in early clinical trials maybe looked at a range of doses and dosing regimens.

Let me put this up, and what you should see in a moment -- can I have the dose-response, please? Okay. What you should see here is the dose response on the X-axis, where with increasing doses, we see that the TTR reduction decreases to a maximum level. And indeed, the dose that we studied, 0.3 milligrams per kilogram, this is the maximum portion of the dose-response curve.

Additional doses are not expected to yield higher or additional TTR reduction, and this has been confirmed in the polyneuropathy patients in APOLLO, where it was shown to be safe and efficacious, and therefore, we selected the same dose for cardiomyopathy because we know this is just a different phenotype of the same amyloid disease.

I hope that answers your question.

DR. BUTLER: Thank you.

Are there any other comments for any of the five discussion points, or any last questions for the FDA or the applicant before we conclude and move on to question 6, which is a voting question?

(No response.)

DR. BUTLER: Hearing none, we will -- Dr. Thadhani, please go ahead.

DR. THADHANI: Thank you. Sorry about that. I couldn't find the button. Just to go back to Dr. Stockbridge, you clarified in terms of methods of approval, primary or accelerated. Was there any discussion on second-line treatment, meaning after first agent doesn't work, as a potential rescue

therapy, with the observation that the patient continues to decline, as we've heard over and over again, which in this inexorable disease seems to be common. Second line treatment, if you could just comment on that. Thank you.

DR. STOCKBRIDGE: Yes. I think if you happen to vote in the next question in favor of approval, you can clarify that's what you had in mind. It is possible to grant somebody a second-line use, but it's a little funny since tafamidis has a different claim than this could possibly have, and no tolerance problem at all, as far as I'm aware.

DR. THADHANI: Thank you.

DR. BUTLER: Thank you, Dr. Stockbridge.

Any further comments or questions?

(No response.)

DR. BUTLER: Hearing none, we will move on to question 6, which is a voting question. Before I read the stem, I will invite Dr. Joyce Frimpong to please provide us with some instructions for voting.

DR. FRIMPONG: Thank you, Dr. Butler.

This is Joyce Frimpong, DFO. Question 6 is a voting question. Voting members will use the Zoom platform to submit their votes for this meeting. If you're not a voting member, you'll be moved to a breakout room while we conduct the vote. After the chairperson reads the voting question into the record and all questions and discussions regarding the wording of the vote question are complete, we will announce that voting will begin. A voting window will appear where you can submit your vote. There'll be no discussion during the voting session.

You should select a button in the window that corresponds to your vote. Please note that once you click the submit button, you will not be able to change your vote. Once all voting members have selected their vote, I will announce that the vote is closed. Please note that there will be a momentary pause as we tally the vote and return non-voting members into the meeting room.

Next, the vote results will be displayed on

the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the list, and each voting member will state their name and their vote into the record. Voting members should also address any subparts of the voting question, including the rationale for their vote.

Are there any questions about the voting process before we begin?

(No response.)

DR. FRIMPONG: Since there are no questions, I will hand it back to Dr. Butler, and we can begin.

Back to you, Dr. Butler.

DR. BUTLER: Very well. Thank you very much. If there are no further questions, can we have question 6? This is a voting question. Do patisiran's benefits outweigh its risk for the treatment of ATTR cardiomyopathy?

After all the votes are registered, we will go through everybody who will declare their vote and will also give a rationale at that point. If

you voted yes, you will have the opportunity to describe the patient population, the clinical meaningful benefit, and how the clinical meaningfulness was established, and if you voted no, provide recommendations for additional data and/or analyses that may support a positive benefit-risk assessment of patisiran for the treatment of ATTR cardiomyopathy.

So again, the voting stem is, do patisiran's benefits outweigh its risk for the treatment of ATTR cardiomyopathy? Are there any clarifications or issues related to the wording of the stem?

(No response.)

DR. BUTLER: If there are no further questions or comments concerning the wording of this question, we will now begin voting on question 6.

DR. FRIMPONG: We will now move non-voting participants to the breakout room.

(Voting.)

DR. FRIMPONG: Voting has closed and is now complete. For the votes, we have 9 yeses, 3 noes,

and no abstentions.

Dr. Butler, I'll hand it back to you.

DR. BUTLER: Great. Thank you very much.

Now we will go down the list and have everyone who voted state their name and vote into the record. You may also include the rationale for your vote, and we'll start with the first person, Dr. Kasper.

DR. KASPER: This is Ed Kasper. I voted yes. Dr. Cella used the term "light wind," and I think he characterized this perfectly. There is a light wind for benefit and no wind for risk. So if you're asking do benefits outweigh risks, the answer is, yes, it does.

It would have been a more difficult question to answer, is there clinically meaningful benefit versus risk, but that's not what the question asked.

DR. BUTLER: Thank you very much.

Dr. Peterson?

DR. PETERSON: Sorry for the delay. Yes, I don't disagree with the last speaker. I think that

the decision on my part came down to benefit being defined in my mind by clinically meaningful benefit. Statistical significance was clear. The magnitude of benefit was small.

Does a functional outcome measure matter for approval? I think that's an important metric for patients and should be a reason for approval. I just felt that the differences here were quite small and bordered very closely into the clinically not meaningful category or wasn't clear to be a clinically meaningful category to get approval, in my sense.

I do believe that some changes in the study design that we talked about, I think summarized well by Dr. O'Connor, clarified the information that is needed. That partly also weighed in on my decision. I think it will be important to get more information here, and the need for another study will motivate obtaining that information in those populations for which we don't have those answers.

DR. BUTLER: Thank you, Dr. Peterson.

Dr. Kovesdy?

DR. KOVESDY: Yes. Thank you. I voted yes. The reason being is that the applicant performed a clinical trial based on discussions with the FDA. They followed the instructions. The study was well conducted. It had an excellent internal validity, and in the end proved efficacy and safety of the study drug.

There has been uncertainty about the clinical meaningfulness. What I heard is that there is no clear answer to this. There is no clear metric. The FDA did not provide an a priori metric to the company to follow during the trial and, in my opinion, this came down to the context and patient population. In the studied patient population, where progression of the used metric was relatively slow, the improvement noted with the intervention could be interpreted as clinically meaningful. Thank you.

DR. BUTLER: Thank you very much.

Dr. Bairey Merz?

DR. BAIREY MERZ: Noel Bairey Merz. I voted no, dominantly because I did not feel like there

was benefit. Again, issues with both the FDA and the sponsor perhaps could have been better designed for clinical relevance thresholds, but using existing clinically relevant thresholds, neither of them met what we typically use in cardiology, so I answered no because of the lack of benefit.

It was offset not by risk, but in my mind also by potential harm. I agree with the concern that opting out of one formulation for another one that may or may not be perceived as better is a potential harm, as well as the intravenous costs and the time and effort among the patients and the providers, so that did influence my decision. My counsel would be both the FDA and the sponsor work together to establish metrics. It is possible that the existing data set of course could be followed longer. I think we were all enthusiastic about seeing the possible breeze that could be extended beyond the longer follow-up, and then as mentioned, possibly a new trial because of that promise. Thank you.

DR. BUTLER: Great. Thank you very much,

Dr. Bairey Merz.

This is Javed Butler. I voted no. I certainly struggled with this vote. My no vote absolutely does not reflect that the disease state is not important, or that there is not an unmet need, or that there is not a potential with the therapy. The reason I voted no was largely because I wasn't sure whether the benefits were clinically meaningful in the context of the study design and how the study was done.

We do realize that in certain circumstances, one trial does lead to approval of a therapy. For instance, in the APOLLO study, the primary endpoint was met with a p-value of 0.001. Here, the p-values for the two endpoints that we have discussed were 0.04 and 0.02, so they were relatively a marginally positive study, and they were relatively a marginally positive study in light of a cap that was put on tafamidis. And if tafamidis use was more liberal, perhaps the studies would not have been positive.

All the analytic issues that we have

discussed, they may not be as much of a concern if the benefits were more robust, but in the absence of more robust benefit, these analytic issues become a little bit more important. So as I mentioned in my comment section, whether this should be a first-line therapy versus tafamidis is an open question, but the trial was not designed to answer this question.

Whether there are incremental benefits, and a dual therapy would benefit patients more, that's where most of the concerns have come up in this study to begin with. And finally, whether the non-responders of tafamidis should be given a second choice, to me, that question was also not satisfactorily answered because the non-responders to tafamidis may have something about their biology, that they may have more progressive disease non-responsive to therapy, and the fact that there was a NYHA class III interaction also affected my decision.

So either of the results were modest, but there was no tafamidis interaction -- or if there

was a tafamidis interaction, but the results were really robust, I would have voted differently, but in the presence of both, I voted no. I did not have any significant safety concerns.

Dr. Abernathy?

MS. ABERNATHY: I voted yes. I really struggled with it, too. I do not disagree with a lot of the caveats people have expressed, and the wishes for a better design study and more clarity perhaps around the complex nature of what exactly is being measured, and how. Nevertheless, like Dr. Kasper, the mild wind was enough to really sway me. It just feels like it's at least something, and there were no apparent risks, so that swayed me towards the more positive side.

DR. BUTLER: Thank you very much.

May I request all the colleagues who have voted yes, which is the rest of the panel, there was a second part to the discussion as well, that if you have voted yes, what is the clinical meaningfulness of the result, and which patient population you would recommend, and how clinical

meaningfulness was established? So if you can answer those aspects as well in your yes vote, that will be helpful.

Dr. Thadhani?

DR. THADHANI: Thank you, Dr. Butler. I voted yes. We're dealing with a rare disease with few options and devastating consequences. I don't think anyone would debate that. We heard from clinicians loud and clear, and from patients for that matter, that options and alternatives are critical, and that there is continuous decline of cardiac function and worsening of disease in a number of patients that have received the current standard of care.

The sponsor could not -- or may have -- but certainly had to deal with what was relevant at the time, and that is standard of care had not been established, and certainly then, appropriately as we heard from the agency, capped the number of patients with tafamidis on this particular study. So for those reasons, benefit outweighed the risk for me, given the minimal risk. Benefit clinical

meaningfulness, again, is subjective, as we heard numerous times. That said, we know it's minimal.

To your question, Dr. Butler, we did not see, at least from the data provided, a benefit, disappointingly, for women, for African Americans, and certainly among individuals that were receiving tafamidis. And I would certainly urge, which I'm sure they will do, discussions between the agency and the sponsor to take into account those populations that either did not benefit or did not appear to have any additional benefit.

We also heard there was no evidence of additive benefit or synergistic effect. Albeit theoretical, which would make sense, we did not see any data towards that end, and I suspect those populations who did not benefit, in conjunction with the data presented on the lack of a synergistic benefit, should guide the discussions between the sponsor and the agency. Thank you, Dr. Butler.

DR. BUTLER: Great. Thank you very much.

Again, that was very helpful. If you can

address these two issues of the clinical meaningfulness and not statistical, and also which patient population for the yes vote.

Dr. Cella?

DR. CELLA: Thank you. David Cella. I voted yes. Like others have said, and maybe all of us, I struggled quite a bit and really was on the fence through almost all of the meeting, but at the end of the day, a few things swayed me towards the yes vote, and one of them was the cumulative distribution function that was pretty consistently in favor of the treatment, not deviating anywhere along the way.

I did ask for additional analysis of the 10-point change in the KCCQ, and that was very helpful for me because while I'm not willing to acknowledge 5 points as clinically meaningful, I am willing to acknowledge 10 as very likely to be a clinically meaningful individual change. There was still a benefit to the treatment that I think translated to a number needed to treat of around 12, and from what I heard from the patients in the

public, and also clinicians both in the public comment as well as on the panel, and from the sponsor's perspective, there does seem to be a real desire to have this available.

I do hope that clinicians, and I expect that clinicians will, counsel patients when talking about treatment options. As for who to target for this, being a non-physician -- I'm really out of my depth here -- I don't have a problem, for example, saying give tafamidis first because of the same endpoints. Unless there's some reason, biological reason, to think otherwise, the very same endpoints in the tafamidis trial were much more powerfully better than here in this trial.

So I'm not sure why a clinician would not recommend tafamidis to start with, and then therefore consider this in tafamidis failures as an example, realizing different mechanisms and probably other reasons to be concerned about that approach since it's not actually been studied. But I do think the fact that the same endpoints were used in both trials, and the vast difference in the

benefit of each, is to me compelling enough to suggest that there be some discussion between the agency and the sponsor on appropriate use and educational material. Thanks. I'll stop there.

DR. BUTLER: Thank you very much.

Dr. O'Connor?

DR. O'CONNOR: Chris O'Connor. I voted yes. As Ed Kasper said, this is a bunt single versus a home run of tafamidis. I voted yes because I believe that we could develop the proper swim lane with the agency for the use of this, and particularly in the tafamidis naïve patients. I want to compliment the sponsor for the conduct of the trial and impressed how they were able to power through the COVID and get a meaningful trial, and they designed the trial, and they met their primary endpoint; albeit, the efficacy signal was small.

I was disappointed with some aspects of the design: the cap; the short-term follow-up; the lack of a progressive clinically integrated endpoint with a win ratio incorporated with the 6-minute walk; and the unclear utilization of

adaptive monitoring design, which could have resized the trial to perhaps have given us a stronger signal.

I am impressed that all the signals -- echocardiographic biomarkers, particularly NT-proBNP and troponin, imaging, and the pooled post hoc clinical events -- all line up. So even though none of them, except maybe the biomarkers on imaging, were strong, they all line up in the right direction, and mechanistically that's very satisfying to me, and of course the safety has been well recognized.

So I would say that in the tafamidis naïve patients, how we define that -- whether it's excess cost, or intolerance as a second-line drug -- if we do that, given what we know, in my opinion, about third-party payers and the small market that that would provide, I think the sponsor would work, and would be highly encouraged to conduct a much more robust clinical trial that would stratify on tafamidis use but allow that use to be what is in practice, whether that's 50 percent or 75 percent

baseline, empowered sufficiently in those two strata with a composite clinical endpoint using a win ratio type methodology. Thank you.

DR. BUTLER: Thank you very much.

Dr. Roy-Chaudhury?

DR. ROY-CHAUDHURY: Yes. Thank you for the opportunity. I voted yes. It was not a completely clear decision. I would say that in my own mind, I was 60 percent yes and 40 percent no. What I will do in my comments is just go through the reasons why I voted yes, and within that, try and answer, Dr. Butler, the two questions that you're particularly interested in.

So I voted yes because there's a clear unmet clinical need. I voted yes because I felt that there potentially was durability of results versus inexorable progression. I understand that that could be different. I voted yes because, as Dr. O'Connor has said, there was this very nice alignment or unidirectionality of the signal. I voted yes because I felt that there were no safety concerns of note, and I think in the real

world -- and this issue came up in a couple of points -- is the Medicare Part B/Part D issues, the payment issues, and the potential of patients getting access. And again, I know that's not completely a key clinical issue, but I think it's out there for all of us.

Coming to the two questions that you had asked about, the patient population and the clinical meaningfulness, I think clearly patients that have both polyneuropathy and cardiomyopathy could be one group that this could be used first. Tafamidis failures, obviously, and we've discussed this, would be the other group, and the point about waiting the right amount of time would be very important.

On clinical meaningfulness -- and I just want to expand a little bit on this -- I have a huge amount of sympathy listening to everybody, both for the FDA and the sponsor, with regard to this issue of what is clinically meaningful. I think we don't have the information that would allow us, really, to create cutoffs for what is

clinically meaningful or not. And I really want to applaud, I would say, the FDA, coming particularly from the kidney area, just in the context that they have agreed in their guidelines to have very clinically oriented primary endpoints. I think that's a huge, huge plus.

But putting it all together, I did give the benefit of doubt for this question to the sponsor, but what I would like to suggest, and this is similar to what Dr. Merz said, is that I think there is such a great opportunity for the FDA, and maybe multiple sponsors together, to really try and create an innovation substrate in this area that will ultimately be able to answer all of these questions. Whether it's another trial, whether it's a mandated registry linked to payment, perhaps, as has been done as I understand in the CDRH and device world, but getting more information about the anchors, about what is clinically meaningful, about the true relevance of durability and slopes, and really creating opportunities for more risk stratification in this area and

opportunities for research, could that be done in the context or under the overall umbrella for further research for a registry?

I'm smiling a little bit here. I'm trying to paint the FDA as a public health agency for innovation in a way, but many times you've done so well in that regard, so I do think that there is an opportunity here. If we had this sort of information, then in this area at least -- and I'd go back to the initial analogy -- maybe we would be able to convert this light breeze into a strong wind or, alternatively, demonstrate a complete stillness down the road in this area.

So I will stop there, and I do want to say I learned so much from everybody's comments, so thank you so much for that.

DR. BUTLER: Thank you very much.

Moving on to Dr. Smith, again, the robust discussion that we're having in terms of people's perspective for a yes vote, describing the clinical meaningfulness, the way it was established, and the patient population this may be attributable to,

please respond to those questions as well.

Dr. Smith?

DR. WILDER SMITH: Hi. Yes. Thank you. I voted yes, and the rationale for that decision, much like my colleagues, I was listening to the evidence throughout and the perspectives presented throughout the day, and it was difficult to make a decision. But for me, the reason came to that we saw a modest but consistent effect and benefit on the 6-minute walk test, the primary endpoint, and a small intervention effect on the secondary outcome of the KCCQ-OSS measure, and that was demonstrated.

So the question of clinical meaning was debated at length with really excellent information provided by the FDA and helping to provide a rich foundation for this committee to consider the evidence. We could certainly debate the meaning more extensively; however, given that there were no safety or tolerability concerns, as others have stated, it seemed that the benefits really outweighed the risks. And again, Dr. Kasper I think was the first to say that the question that

we were asked about was whether or not the benefits outweighed the risk, which I felt that they did.

Additional information related to effects after 12 months would have been highly beneficial, as would have been a greater sample size to present findings across demographic subgroups. I agree with Dr. Thadhani and others that there were specific subgroups that did not show clear benefits -- African Americans, women, and those on tafamidis -- and I agreed with Dr. O'Connor and others that a large trial would be highly beneficial, particularly powered for examination of these subgroups.

I did also want to echo some of the other advisory committee members' statements regarding concerns about interpretation of benefit to patients relative to tafamidis. I'm not a clinician, and my field is actually not in cardiovascular disease, but it is in patient-reported outcomes and in functional status.

Listening to the concerns that folks had, I'm also in a healthcare delivery research area

where we think about how these kinds of evidence-based decisions affect patients and clinicians in real time as they're making decisions, so the concerns that have been raised, to me, suggest that there's a need to ensure that the communication about what and how much benefit has been found is clearly articulated to the public, and specifically to support clinicians and patients in understanding and not overstating the benefits. That is beyond the scope of what this committee was asked to do, but given my colleagues' comments, I wanted to echo them because I think that's really an important part of how this information is used in the real world, and I will stop there. Thank you.

DR. BUTLER: Thank you, Dr. Smith.

Dr. Moliterno?

DR. MOLITERNO: Yes. Thank you, Dr. Butler. David Moliterno. I appreciate we're a little bit over time here, so I'll try not to talk too long, and I'm thrilled not to have the responsibility of trying to summarize everything like the chair has.

In short, this was a binary vote, but I think to the point of everyone who spoke, I think our confidence intervals all overlap, so I think we're all saying much the same thing. For me personally, I was impressed. Well, let me just say thanks to the sponsor. I thought they did a very nice job with their presentation today. I agree with Dr. O'Connor; I think the study was executed very well, but I have concerns, reservations, about the study design.

I think, overall, I was impressed by the cumulative distribution curves that did show benefit, albeit quite small, along the entire course. I am bothered, as the last speaker, Dr. Smith, said, by a large proportion of the patients, at least in subgroups, as I mentioned earlier, who did not show benefit, so I do think the sponsor will be obligated to do more.

So is this a bunt single? Yes. But do I have concerns about a foul ball going forward? I really do. I think there is potential benefit going out further. Had we stopped the tafamidis

studies at one year, we wouldn't have seen the mortality benefit; nonetheless, we have seen a mortality benefit, and a substantial one, so I would hate to see this drug get marketed or pushed forward as an alternative to tafamidis.

I appreciate Dr. Stockbridge's comments that we've got two different indications going forward here. The sponsor looking at symptom improvement, as they stated in their label, or quality-of-life improvement, they did show that without risk, so that's a good thing, but I would hate to see any unintended consequences if patients don't get put on tafamidis because of this drug, so I do think there could be a harm.

I think the great benefit could be is that if we get another drug company here who can increase education because I do think that the cardiac amyloidosis is underdiagnosed and undertreated, so there potentially could be a win-win going forward. I could keep talking, but I'll stop there, Dr. Butler. Thank you.

DR. BUTLER: Thank you very much,

Dr. Moliterno.

These extended comments are really helpful, and I think will help in putting everything in perspective. If I may, I sort of reneged in my responsibility for the first few colleagues who voted yes and expanding on these issues about how they perceive clinical meaningfulness, and how the meaningfulness was assessed, and the patient population where it will be used. I know that we are over time, but I'll just take a quick liberty for 5 minutes and go back to the first three yes votes, and if they can expand on these issues.

Dr. Kasper, may I ask you to expand on this a little bit?

DR. KASPER: Yes, and I'm sorry. Again, Ed Kasper. I'm sorry that I didn't pick this up myself. I should have answered the questions that were asked. In terms of the clinical meaningfulness, I think it's difficult to know just how clinically meaningful this is. We heard conflicting reports from the FDA and from the sponsor as to just how clinically meaningful. If

it is clinically meaningful, it's probably pretty minimally clinically meaningful but, again, it still outweighs the risks of a drug that apparently is minimally risky.

In terms of the other groups, I see no data here whatsoever that supports any use other than as monotherapy. This really doesn't address the use as a rescue therapy. It doesn't address the use as plus tafamidis, so I see it as being a fairly niche kind of thing. If I were to put on my other hat of ACC AHA guideline writer from years back and you asked me what level of evidence would I give this, or what class of recommendation, this wouldn't be a 1, and it wouldn't be a 2A. It might be a 2B. The level of evidence is not high here.

So that's my thinking behind this. Thank you all for a very interesting day.

DR. BUTLER: Thank you very much.

Dr. Kovesdy, may I request you to expand on your yes vote a little bit as well?

DR. KOVESDY: Yes. I believe I did. I mentioned that clinical meaningfulness would be

context dependent, and I view it in that context in that the study population was one that had relatively earlier stage disease and slow progression of the studied outcome. And in that particular context, the magnitude of the effect that was displayed by the investigational agent could be considered clinically meaningful since progression approached essentially natural progression and age-dependent progression in this population.

I would echo and very much agree with my peers here who emphasize that an indication should be limited very much to what was studied in this particular trial because I, too, am worried about expanding and reading too much into what this drug can and cannot do. So based on what was presented to us, I voted yes, and I would not agree to expand this to indications such as combination therapy, or somehow taking over the place of the other agent, which has more data. Thank you.

DR. BUTLER: Thank you.

And Ms. Abernathy, do you have any further

comments to expand?

MS. ABERNATHY: My comments really are in line with those we just heard. I think the thing for me, the thing that would make it much more convincing would be a longer duration of clinical trials, and perhaps we would see either more positive or perhaps steady or more negative. But given what we have heard and what some of the other voters have suggested about the direction of the indicators, it seemed to me to be a reasonable thing to consider, that if it were looked at further, longer, perhaps we would have more specific data.

Given that, my vote yes also comes with parameters, the context, yes. I could imagine that this will be appropriate for people who cannot take tafamidis for whatever reason, as I mentioned previously, but beyond that, I do think that more information, more data, is necessary. Again, the yes vote really came about because there didn't seem to be any risk, and there did seem to be a positive trend. Thank you.

DR. BUTLER: Well, thank you very much.

Let me see if I can summarize. I think it's pretty interesting, to Dr. Moliterno's point, there is actually a substantial overlap in the comments for both those who voted yes and those who voted no, and it appears that despite the fact that the comments and the concerns are very similar, the differentiating factor was the weight that people put into the fact that this is somewhat of a rare disease with an unmet need, and that swayed the individuals, but the interpretation of the data and the limited robustness of the data was pretty much mentioned by everybody.

We did have a robust discussion on statistical significance versus clinical meaningfulness and had significant concerns by the way the data were analyzed to assess if clinical meaningfulness was robust or appropriate or not. And then finally, the data that we did get at the end of that, those statistically positive results, were they truly clinically meaningful or not? The answer to that question becomes a little bit more

difficult because we don't have standards from precedence by which we can say that for this particular disease state, this should be the standard. And in the absence of a KCCQ standard or the absence of a 6-minute walk test standard, we are left with this statistically positive result.

Then the way the voting question/stem read, the issue was benefit as opposed to risks, and because the risks were felt to be minimal, then any benefit was felt to be a benefit that was worth it, but was certainly commented by all, regardless of whether people voted yes or no, that the benefits were modest.

There were discussions, obvious discussions, related to multiple subgroups, whether that was race, or gender, or geographic related, but, obviously, the biggest one was related to the use of tafamidis. I think the most important comment perhaps that I heard was that it will be a harm if somehow the basis of the data that we had were to be used in preference ahead of tafamidis, and that would be not an advisable thing to do; and if it is

approved, how to place it in the patient population who are either not able to obtain tafamidis, or tolerate tafamidis, or respond to tafamidis, although the response question was in everybody's mind, how do we define it?

Multiple study-related comments were made of how the study could have been done better, not only in terms of power, and size, and endpoints that were chosen, including the possibility of a composite endpoint about adaptive designing, but also perhaps one of the most important comments that came up is that longer term data beyond 12 months would have been really helpful to truly see what the benefit is, and having this artificial cap on tafamidis made it really difficult to interpret the result, regardless whether people voted yes or no.

So that was the summary of what I heard from everyone, so I think this is time to close the meeting and adjourn. I would really like to thank the applicant and congratulate them for conducting the study and for their presentation. I also would

like to thank the FDA for their thoughtful comments and thoughtful analysis as well, and all the public comments that were received in the open public hearing and all the presenters, thank you very much. Those comments are always very meaningful because they take us beyond the realm of statistics and numbers, and puts a human face to what we are dealing with.

Finally, I really would like to thank all the panel members for their incredibly thoughtful comments and all the time and efforts they put into this discussion, both preparing prior to the meeting and during the meeting as well.

So before I formally adjourn the meeting, I would just like to ask if the FDA has any final comments to make.

DR. STOCKBRIDGE: I can only echo what you just said. I very much appreciate the time and effort that all of the committee put into this, and I'm particularly grateful for the articulate explanation for how people voted and what they thought of things. So this is going to be very

helpful to us. Thank you all.

Adjournment

DR. BUTLER: Thank you very much, Dr. Stockbridge, and at this point, we will formally adjourn the meeting. Thank you very much.

(Whereupon, at 4:19 p.m., the meeting was adjourned.)