FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE (EMDAC)

Thursday, November 14, 2019

8:01 a.m. to 4:28 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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P R O C E E D I N G S

(8:01 a.m.)

Call to Order

Introduction of Committee

DR. BURMAN: I would like first to remind everyone to please silence your cell phones, smartphones, and other devices if you have not already done so. I would also like to identify the FDA press contact, Monique Richards.

If you're a present, please stand. Thank you.

My name is Ken Burman. I'm the chairperson of the Endocrinologic and Metabolic Disease Advisory Committee, and I will be chairing this meeting. I will now call this meeting to order. We will start by going around the table and introduce ourselves. We will start the FDA to my far left.

DR. YANOFF: Good morning. Lisa Yanoff, acting director, Division of Metabolism and Endocrinology Products at FDA.

DR. SHARRETTS: John Sharretts, acting

deputy director, Division of Metabolism and Endocrinology Products.

DR. CHOWDHURY: Iffat Chowdhury, DMEP, clinical reviewer.

DR. CRACKEL: Roberto Crackel, statistical reviewer for the Division of Biometrics II.

DR. REN: Yunzhao Ren, Clinical Pharmacology, DIIP, OTS.

DR. BRITTAIN: Hi. I'm Erica Brittain. I'm a statistician at National Institute of Allergy and Infectious diseases, NIH.

DR. DE LEMOS: James de Lemos. I'm a cardiologist at UT Southwestern in Dallas.

DR. LOW WANG: Cecilia Low Wang, endocrinologist and professor of medicine at University of Colorado.

DR. KRAFT: Walter Kraft, clinical pharmacologist at Thomas Jefferson University.

DR. FAJICULAY: Jay Fajiculay, acting designated federal officer of the EMDAC, FDA.

DR. BURMAN: Ken Burman, chief of endocrinology at MedStar Washington Hospital Center

and professor of medicine at Georgetown University in Washington D.C.

DR. ELLENBERG: Susan Ellenberg, professor of biostatistics and medical ethics and health policy at the Perelman School of Medicine, the University of Pennsylvania.

DR. WILSON: Peter Wilson, professor of medicine, public health, Emory university.

DR. NEWMAN: Hello. I'm Connie Newman. I'm an endocrinologist and adjunct professor of medicine at New York University School of Medicine.

DR. WEBER: Tom Weber, endocrinologist at Duke University in Durham, North Carolina.

DR. KONSTAM: Marv Konstam, Tufts Medical Center, cardiologist.

DR. NASON: Good morning. I'm Martha Nason. I'm a biostatistician at the National Institutes of Health, National Institute of Allergy and Infectious Diseases.

DR. ORTEL: Tom Ortel, chief of hematology at Duke University in Durham, North Carolina.

DR. YANOVSKI: Jack Yanovski, chief of the

section on growth and obesity in the intramural NICHD, one of the national institutes of health.

DR. CHRISCHILLES: Betsy Chrischilles, professor of epidemiology, University of Iowa, College of Public Health.

DR. MEININGER: Gary Meininger, endocrinologist, head of pipeline development at Vertex and the industry rep for EMDAC.

DR. BURMAN: Thank you. Dr. Posner?

DR. POSNER: Philip Posner. I'm the patient representative. I have [indiscernible] and atrial fibrillation, and I'm a retired professor of physiology and pharmacology with a specialty in cardiac electrophysiology.

DR. BURMAN: Thank you for joining us by phone. Throughout the meeting, if you don't hear anything particularly well, just let us know, and we'll try to clarify that.

DR. POSNER: I will. Thank you.

DR. BURMAN: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite

strongly held. Our goal is that today's meeting will be a fair and open forum for 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.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the 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 topic during breaks or lunch. Thank you.

Now I'll pass it to Dr. Jay Fajiculay, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. FAJICULAY: The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic 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 the 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 the agency's need for a special government employee's services outweighs his or her 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 interest 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 discussion of the supplemental new drug application 202057 supplement

1 035 for Vascepa, icosapent ethyl capsules for oral
2 administration, sponsored by Amarin Pharma, Inc.,
3 for the following proposed indication: to reduce
4 the risk of cardiovascular events, as an adjunct to
5 statin therapy in adult patients with elevated
6 triglyceride levels, 135 milligrams per deciliter
7 or greater, and other risk factors for
8 cardiovascular disease, based on the results from a
9 clinical study entitled, A Study of AMR101 to
10 Evaluate Its Ability to Reduce Cardiovascular
11 Events in High Risk patients with
12 Hypertriglyceridemia and on a Statin.
13 The primary objective is to evaluate the
14 effect of 4 grams per day AMR101 for preventing the
15 occurrence of a first major cardiovascular event,
16 REDUCE-IT.
17 This is a particular matters meeting during
18 which specific matters related to Amarin's sNDA
19 will be discussed. Based on the agenda for today's
20 meeting and all financial interest reported by the
21 committee members and temporary voting members, no
22 conflict of interest waivers have been issued in

connection with this meeting. To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Gary Meininger is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Meininger's role at this meeting is to represent industry in general and not any particular company. Dr. Meininger is employed by Vertex Pharmaceuticals.

We would like to remind the 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. BURMAN: Thank you.

We will now proceed with the FDA's opening remarks by Dr. John Sharretts.

FDA Introductory Remarks - John Sharretts

DR. SHARRETTS: Good morning. My name is John Sharretts. I'm the acting deputy director in the Division of Metabolism and Endocrinology Products. Thank you for attending today. The purpose of today's meeting is to discuss the benefits and risks of Vascepa for a new indication, to reduce the risk of cardiovascular events, as an adjunct to statin therapy in adult patients with elevated triglyceride levels and other risk factors for cardiovascular disease.

In support of the new indication, the applicant has submitted the results of the reduction in cardiovascular events with EPA interventional trial, abbreviated as REDUCE-IT. The proposed indication has never been approved for any other lipid-altering drug and would have the

potential to impact the health of a large portion of the U.S. population at risk for cardiovascular events who may be eligible for therapy.

Vascepa is an Omega 3, polyunsaturated fatty acid drug product derived from fish oil. It contains purified eicosapentaenoic acid ethyl ester, also known as icosapent ethyl or EPA. Vascepa is also referred to by its investigational product identifier AMR101 in discussions of clinical trial data.

Vascepa was originally approved in the U.S. in 2012 as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia, a population that is at increased risk of acute pancreatitis. Triglyceride lowering alone is not considered a surrogate endpoint for cardiovascular risk reduction, and the applicant conducted the REDUCE-IT trial to investigate the effect of AMR101 on major adverse cardiovascular events.

The REDUCE-IT trial was a randomized, double-blind, placebo-controlled trial of adult

patients with controlled LDL-C levels and elevated triglyceride levels on statin therapy. The population consisted of two cohorts of patients. Cohort 1 included patients aged 45 and older with established cardiovascular disease and accounted for about 70 percent of patients.

Cohort 2 included patients aged 50 and older with type 2 diabetes mellitus and at least one additional risk factor for cardiovascular disease. FDA agreed with the trial design and methods, including two protocol amendments instituted during the trial.

The FDA review team generally agrees with the applicant regarding major efficacy and safety findings in the trial. AMR101 reduced the risk, compared to placebo, of the primary endpoint, a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization, and coronary revascularization.

The safety profile was generally consistent with current labeling except for two new safety

issues that emerged in the trial. AMR101 was associated with an increased risk of atrial fibrillation or atrial flutter and an increased rate of bleeding events compared to placebo. Safety concerns, however, did not appear to outweigh the observed benefits.

Nonetheless, the FDA has several concerns about REDUCE-IT that warrant public discussion prior to a final action on the supplement. One major limitation of the data is the reliance on a single trial to support the new indication. As I noted previously, no other lipid-lowering agent is approved for a similar indication.

Additionally, observed patterns of lipid and inflammatory biomarkers, both in the REDUCE-IT trial and in previous trials conducted by the applicant with the same placebo product, have led to a hypothesis that there is a drug infraction between mineral oil, the major component of placebo, and statin drugs that resulted in an increased risk of cardiovascular events in the placebo arm of REDUCE-IT versus an inert true

placebo.

Although the FDA review team could not conclude definitively that mineral oil interfered with statin absorption, several lines of evidence support the plausibility of an interaction. Today's presentations will address the potential effect of mineral oil on LDL-C and the potential effect of the observed LDL-C increase in the placebo group on clinical outcomes.

Considering the trial limitations, FDA also has concerns regarding the robustness of the data to support all individual components of the primary endpoint such as cardiovascular death. Separately, FDA disagrees with the applicant regarding the population in whom AMR is effective. The applicant's proposed indication does not address the presence or absence of cardiovascular disease; presence or absence of diabetes in patients without cardiovascular disease; age; LDL cholesterol levels; or optimization of statin therapy.

The REDUCE-IT trial, in contrast, included patients with cardiovascular disease, plus a cohort

of patients aged 50 and older with diabetes, additional risk factors for cardiovascular disease, and LDL cholesterol levels optimized mostly with moderate or high intensity statins. As written, the indication for Vascepa would apply to a group of patients with a potentially different benefit-risk consideration than those studied in REDUCE-IT.

Now, I will turn to today's agenda. After my introduction, the applicant will present to you their view of the results of the REDUCE-IT to support the proposed indication. Presentations by the FDA reviewers will follow. From the FDA, you will hear from Dr. Iffat Nasrin Chowdhury, the clinical reviewer; Dr. Roberto Crackel, the statistical reviewer; and Dr. Yunzhao Ren, the clinical pharmacology reviewer.

You will have the opportunity to ask clarifying questions following each set of presentations. After that, we will break for lunch and return for the open public hearing. Then we will move on to the discussion points, which I will

introduce now.

The first question addresses the efficacy results from the REDUCE-IT. We ask that you provide your interpretation of the overall strengths and limitations of the data. Your discussion may address the issues we identified or other issues you consider important, based on the data presented. We ask that you describe your confidence in the overall trial results and the robustness of the data regarding the individual components of the primary and secondary endpoint, including the effect of AMR101 on cardiovascular mortality.

The second question asks you to discuss your level of concern about the new safety findings identified in the REDUCE-IT trial, approaching these issues from the perspective of risk mitigation in the event of approval of the new indication.

The third question addresses the population in whom the benefit-risk assessment is favorable, given the population studied and compared to the

indicated population proposed by the applicant. We ask you to consider enrollment criteria and baseline characteristics, as well as the clinical practice considerations necessary to allow sufficient flexibility for prescribers.

Finally, we ask you to vote whether you believe the efficacy and safety of the REDUCE-IT trial support a new indication for Vascepa to reduce the risk of cardiovascular events. If you vote in favor of approval, we ask you to recommend the appropriate indicated population. If you vote against approval, we ask you to provide your rationale and comment on what additional data would be needed for approval.

I emphasize that the details of your comments and discussion following your vote are as important in informing our decision making, if not more important than the vote tally itself. With that, I will stop and turn the program back to the committee chair. Thank you again for your time.

DR. BURMAN: Thank you.

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

Likewise, 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 Amarin Pharmaceuticals' presentation.

Applicant Presentation - Rebecca Juliano

DR. JULIANO: Thanks, folks, for your patience.

Good morning. I'd like to begin by expressing our thanks to the FDA, and especially to the panelists who are here today for the time and effort it took to review the materials and be prepared for the day, and in particular for the discussion that we look forward to having with you today.

My name is Rebecca Juliano. I oversee the clinical operations and development team, as well as the biostatistics and data management team at Amarin, and I'm pleased to start our presentations today.

Regarding the agenda, I'll provide a brief overview of the program history for icosapent ethyl, which is, of course, the therapy we're here to discuss today. Dr. Miller will then present the medical need for the population that was enrolled and studied within REDUCE-IT, which of course is the primary focus of our discussion throughout

today.

Dr. Bhatt will follow to review both the efficacy and safety analysis from REDUCE-IT. Dr. Navar will then discuss the clinical implications of the REDUCE-IT findings, and finally I will provide a few closing remarks. We then look forward to addressing any questions the panel might have. Listed here are the consultants who have joined us today to support panel considerations and discussion.

Now, beginning with the program history, Amarin is a somewhat smaller company that may not be well known to all of you, so we thought it might be worthwhile to just provide a few brief highlights. We've been committed to the leadership of lipid science for over two decades, with a particular interest in the cardiovascular benefit of Omega 3 fatty acids.

Within those efforts, we've supported and contributed to over a hundred scientific publications and presentations, and for over a decade, we've been focused on the development of

Vascepa, which is the commercial name for icosapent ethyl, and it's also known as AMR101 within our clinical studies.

Icosapent ethyl is a highly purified, stable ethyl ester form of eicosapentaenoic acid, also known as EPA, which, of course, is an Omega-3 fatty acid. As shown on the lower right of the slide, EPA is 20 carbons long with 5 double bonds or degrees of unsaturation. EPA is, by definition, an Omega-3 fatty acid because the first double bond is situated 3 carbons from the methyl or N-terminus of the molecule.

You've likely heard of Omega-3 fatty acids in EPA specifically, in addition to different Omega-3 fatty acids. Often the other Omega-3 fatty acids differ from EPA by only a couple of carbons and maybe one or two differences in double bonds.

Those may seem like subtle and, therefore, inconsequential differences, but these seemingly small structural changes can actually have quite large biological impact. Therefore, icosapent ethyl is a unique molecule, and its effects cannot

be extrapolated to other long-chain Omega-3 fatty acids.

The FDA approved icosapent ethyl for use in patients with very high triglycerides in 2012, with very high triglycerides being defined as patients with trigs over 500 milligrams per deciliter. The reduction of very high triglyceride levels proved to support a reduction in the risk of pancreatitis.

Based on clinical studies, including the REDUCE-IT study, we have over 37,000 patient-years of experience with icosapent ethyl, and since icosapent ethyl has been on the market, over 8 million prescriptions have been provided. Across those years, icosapent ethyl has consistently had low postmarketing adverse event rates.

The current indication for icosapent ethyl was based on two studies. These are the 12-week MARINE and ANCHOR studies. The MARINE study focused on patients with very high triglycerides, defined as 500 to 2000 milligrams per deciliter. Patients could but were not required to be on statin in the MARINE study.

The ANCHOR study had patients that were required to be on statin stabilization prior to enrollment, but despite that statin stabilization had persistently elevated triglycerides in the range of 200 to 500 milligrams per deciliter. The MARINE efficacy data set supports the current icosapent ethyl label, along with the safety data sets from both the MARINE and the ANCHOR studies.

This brings us to why there was a need for a cardiovascular outcome study with icosapent ethyl. There are a couple of different potentially confusing areas within the literature that are worth noting.

The first is that icosapent ethyl reduces triglyceride levels, and the very high triglyceride indication is based on that triglyceride reduction. There's a wealth of epidemiological, clinical, and genetic data to suggest that triglycerides are in the causal pathway of cardiovascular disease, and therefore, high triglycerides can be a marker of elevated cardiovascular risk. What is not well established is whether or not triglyceride

reduction will result in a cardiovascular benefit.

Secondly, the REDUCE-IT study was conducted on a backdrop of a number of other cardiovascular outcome studies that administered Omega-3 fatty acids, that on top of statin therapy did not demonstrate a cardiovascular benefit. It's important to note that those studies provided low doses of mixed Omega-3 fatty acids. As mentioned earlier, EPA is unique from other Omega-3 fatty acids, and there's a breadth of literature to suggest that EPA not only lowers triglyceride levels but can provide a number of other potentially cardioprotective effects.

In addition, there was a prior cardiovascular outcome study, the JELIS study, which we will discuss in a little bit more detail today. Within JELIS, a cardiovascular benefit was reported with the achievement of high blood levels of EPA from administration of an EPA-only prescription product available in Japan, and importantly that was on top of statin therapy.

Due to study limitations, the JELIS study

provided supportive but not conclusive data about whether or not these benefits of EPA would be observed in and a broader, multinational patient population, which brings us to the REDUCE-IT study.

Different from MARINE and ANCHOR, which, again, were 12-week biomarker studies, REDUCE-IT was designed as a cardiovascular outcome study. We targeted enrollment of around 8,000 patients with an expanded MACE composite endpoint. Importantly, before randomization, patients were to be stabilized on statin therapy with controlled LDL cholesterol between 40 and 100 milligrams per deciliter, but to still have persistently elevated triglycerides despite that statin therapy, defined between 135 and 500 milligrams per deciliter.

As a brief overview, the critical components of the trial design and of the two protocol amendments were reviewed and agreed by the FDA under a special protocol assessment agreement. The first protocol amendment increased the lower limit of triglycerides from 135 to 200 milligrams per deciliter.

This decision was made in a blinded fashion by the steering committee and Amarin to ensure enrollment of a broad range of triglyceride levels within the patient population enrolled. The second protocol amendment elevated the hard MACE endpoints to the key secondary endpoint position, and this was based on discussions and input with the REDUCE-IT steering committee and from FDA.

REDUCE-IT was a prospective, randomized, placebo-controlled, multinational study. It was conducted in over 8,000 patients and 11 countries with a median follow-up time of 4.9 years. As noted earlier, the primary endpoint, as well as the secondary endpoints, were focused on cardiovascular outcomes as opposed to the earlier 12-week ANCHOR and MARINE biomarker studies.

REDUCE-IT was designed to test the cardiovascular benefit of icosapent ethyl. By design, it cannot answer the larger question of whether triglyceride reduction will consistently result in cardiovascular risk reduction. REDUCE-IT also cannot define whether or not other Omega-3

fatty acids are effective in cardiovascular risk reduction.

Dr. Bhatt will shortly present the REDUCE-IT results, but REDUCE-IT demonstrated a cardiovascular risk reduction in the primary endpoint that was substantial and statistically significant. It also demonstrated reductions within the prespecified testing hierarchy of the secondary endpoints. Results were generally consistent within other tertiary exploratory cardiovascular endpoints and across subgroup analyses. Importantly, icosapent ethyl was overall well tolerated with safety considerations that can be addressed within labeling.

Based on the REDUCE-IT study results, Amarin is seeking a cardiovascular risk reduction indication for icosapent ethyl. We look forward to labeling discussions with the FDA to achieve final indication language and label content that will communicate the REDUCE-IT efficacy and safety results for the patients enrolled in REDUCE-IT. These patients were statin treated with controlled

LDL cholesterol but persistently elevated triglyceride levels. They had either a history of established cardiovascular disease or were high-risk primary prevention patients with diabetes and other risk factors.

Through our presentations and by answering the questions from this panel, Amarin aims to address the discussion topics highlighted by the FDA. At a high level, these topics are, first, the robustness of the efficacy results, including support for our first-in-class cardiovascular outcome indication, mineral oil placebo considerations, the magnitude and clinical relevance of the treatment effect with icosapent ethyl, and the robustness of the individual components of the primary and the key secondary composite endpoints;

Next, the ability to represent the safety findings of atrial fibrillation or flutter and bleeding within a label;

Third, the evidence of cardiovascular benefit within the cardiovascular risk cohort

number 2, namely those who were enrolled specifically based on the presence of diabetes with consideration of age, diabetes, and additional risk factors, LDL cholesterol and triglyceride levels, statin intensity, and other factors;

And finally, the sufficiency of efficacy and safety evidence for a cardiovascular risk reduction indication.

So with that, I will ask Dr. Miller to discuss the unmet need in the REDUCE-IT like patient population.

Applicant Presentation - Michael Miller

DR. MILLER: Good morning. My name is Mike Miller. I'm a cardiologist and serve as the director for the Center for Preventive Cardiology at the University of Maryland School of Medicine. Today I will be sharing my clinical perspectives on the need for icosapent ethyl treatment in adult patients at high cardiovascular risk and who have elevated triglyceride levels in spite of stable statin therapy to control their LDL cholesterol. In terms of my disclosures, I am a member of the

REDUCE-IT steering committee, and I receive consulting fees from Amarin for these services.

It is well established that cardiovascular disease is the leading cause of death in the United States. Every 40 seconds, someone in the U.S. has a heart attack. In that same 40 seconds, another person has a stroke. And even less time than that, someone has died from cardiovascular causes.

So despite providing standard of care, where we manage cholesterol, diabetes, and hypertension, we can all appreciate that heart disease remains a large and growing crisis that, unfortunately, not many add-on therapies have prevailed with proven clinical benefit.

Despite our best efforts with all of the available proven therapies, many of our patients continue to have new and recurrent events. Approximately two-thirds of patients will continue to have what we refer to as residual risk despite LDL control. In other words, a high percentage of patients continue to have recurrent events despite well-controlled LDL cholesterol.

I see high cholesterol and high cardiovascular risk patients on a regular basis and recognize that there are limited options for treating residual risk. It is well recognized that high cardiovascular event rates occur in these patients, and in the past, there have been limited options. In part, this reflects failed cardiovascular outcome trial data for widely used therapies such as niacin and fenofibrate.

As such, there is an urgent need for new treatment options due to the size of both 10-year MACE rates observed in REDUCE-IT like patients that have ranged between 20 to 28 percent. This includes notable CD risk factors beyond LDL control that were within the inclusion criteria in REDUCE-IT, namely persistently elevated triglycerides, prior MACE events, and diabetes.

As Dr. Bhatt will further elaborate upon, REDUCE-IT enrollment criteria, by nature, would also identify patients with other risk factors such as metabolic syndrome and hypertension. As well, convergence of multiple risk factors are often

prevalent in patients with persistently high triglycerides now viewed as a cardio risk enhancer.

As a steering committee member, it is worth noting why we specify persistently elevated triglyceride levels as an inclusion criteria for all REDUCE-IT patients. Elevated triglycerides have long been considered causal with respect to cardiovascular risk. This statement, which is not new, is supported by epidemiological, genetic, and clinical data.

As we demonstrated in the early PROVE-IT study, even in patients that achieve an optimal LDL under 70 milligrams per deciliter, statin-treated patients with triglycerides above 150 have a 41 percent high risk of coronary events as compared to patients with triglyceride levels that were below this level.

Across varying baseline triglyceride levels, you will find this risk association, and this increased risk can present at what is often considered normal triglyceride levels. On the left is a 16-week follow-up of the MIRACL study that

tested atorvastatin versus placebo in patients with acute coronary syndrome. On the right is a long-term Dal-OUTCOMES study that tested dalcetrapib in patients with recent acute coronary syndrome.

If we look at both left and right panels, those individuals at the highest triglyceride levels, either by tertiles or quintiles, had greater likelihood of event over a relatively short period of time or the longer follow-up period. In contrast, those at the lowest triglyceride levels conferred the lowest likelihood of having an event over that period of time, and yet increased risks start to become apparent at TG levels greater than 135 in MIRACL and at levels above 103 in Dal-OUTCOMES.

We also appreciate that the lifetime risk associated with triglycerides, shown on this slide, to the left is incident cardiovascular disease based on analysis of both the ERIC and Framingham study.

Looking across 10-year cardiovascular risk

scores, as triglyceride levels increase from around 70 milligrams per deciliter, the risk substantially increases before beginning to plateau at approximately 200. The longstanding Copenhagen Heart Study on the right, looking at all-cause mortality, also continues to show increase in CV risk that appears to steep and beginning around 80 milligrams per deciliter.

Triglycerides are rather well established as an effective identifier of patients at an elevated cardiovascular risk, but that is not the same as triglyceride being a modifiable risk factor. We do not have sufficient consistent data to understand the extent to which triglyceride lowering might reduce CV risk. As Dr. Juliano just pointed out, there are no studies specifically designated in a hypertriglyceridemia population that have addressed this question.

We do know that high triglycerides correlate with elevated risk, which have been supported by the number of studies, both from an epidemiologic standpoint as well as from the randomization

1 studies, as well as from subgroup analysis of
2 clinical trials. There is also clear evidence that
3 triglyceride-rich lipoproteins promote early
4 atherosclerotic processes, including increased LDL
5 particle concentration and remnant cholesterol
6 deposition.
7 Yet it remains to be determined whether and
8 to what extent triglycerides or triglyceride
9 reduction may be associated or translated into
10 reduced events. This question looms largely
11 because clinical outcome studies of therapies that
12 lower triglyceride levels have not translated into
13 improvement in events. One flaw in these trials is
14 that the patient population studied were not
15 exclusively hypertriglyceridemic.
16 If you'll look at subgroup analysis from a
17 ACCORD-Lipid and AIM-HIGH, subgroups that had high
18 triglycerides and low HDL tended to be at elevated
19 risk, and that risk appeared to be reduced by
20 therapy in those subpopulations.
21 So while there is some evidence that
22 triglyceride lowering therapies may confer CV risk

reduction in an appropriate population, it has not been established that triglycerides are a modifiable risk factor. Therefore, triglycerides can be useful to identify patients at risk beyond standard of care even if we do not know for certain if lowering triglyceride levels will result in CV benefit. The question as a clinician is what can we do to potentially offset that risk?

One such promising line of therapy to offset risk has been Omega-3 fatty acids. Despite some early promising CV outcome studies, later studies in statin-treated patients did not demonstrate a benefit with Omega-3 fatty acids, which has led to apparently mixed signals with regard to the clinical benefit of Omega-3 fatty acids in statin-treated patients.

Early low-dose studies with mixed Omega-3 fatty acids such as GISSI-Prevenzione suggested benefit, however, these studies predated our current standard of care that includes concomitant statin use. So only a small percentage of patients in GISSI were on statins.

Subsequent low-dose, mixed Omega-3 studies do not suggest benefit when added to statin, including the very recent VITAL and ASCEND studies. These large long-term outcome studies included low-dose mixed Omega 3 in either a dietary supplement form or a prescription combination of EPA, DHA, and other ingredients. None of these studies had results which translated into a reduction in cardiovascular risks.

Prior to REDUCE-IT, there was one study, however, that supported the possibility that a higher dose of a purified Omega 3 provides cardiovascular benefit, and this is the JELIS study. Using purified EPA on top of statin in the Japanese population, JELIS was distinct in reporting a cardiovascular benefit. It was also unique to correlate risk-benefit with high plasma EPA levels, supporting the need not only for a high dose but a stable dosage form.

But much like the other studies using therapies that lower triglyceride levels, JELIS did not study patients exclusively with

hypertriglyceridemia, but rather a high-risk population with either preexisting cardiovascular disease or high-risk dyslipidemia. In fact, the baseline triglyceride level for the overall study cohort was not elevated, and the overall triglyceride reduction with EPA therapy was only approximately 5 percent. Therefore, the cardiovascular benefit report in JELIS could not be fully explained by reduction in triglycerides.

JELIS was the first outcome study reporting the cardiovascular benefit of EPA, and the results are presented here. The PROBE design of JELIS meant that it was prospectively designed and randomized with open-label treatment and blinded endpoint adjudication. JELIS patients were randomized to either 1.8 grams a day of EPA plus statin or to statin alone without a placebo.

In a total cohort of 18,645 patients, a 19 percent relative risk reduction was reported, again, with only a 5 percent reduction in triglyceride levels. It is interesting to note that JELIS enrolled 80 percent primary prevention

patients; 69 percent women and patients at baseline had a triglyceride level of approximately 154 prior to statin initiation at baseline.

What might be the potential mechanisms whereby EPA reduces cardiovascular events? Decades of broad clinical and subclinical evidence suggest EPA may be beneficial by virtue of a number of potential factors. They include the reduction of atherogenic remnant particles or triglyceride-rich remnants; along with reduction in inflammation; and platelet aggregability and thrombus formation; and plaque progression and instability; as well as improvement in endothelial function.

In retrospect, JELIS reported that high-dose EPA has cardiovascular benefit, particularly beyond baseline or achieved triglyceride levels. Nonetheless, there was some caveats to the design of JELIS and questions do remain. In particular, will a similar benefit be observed in a double-blind, placebo-controlled study? What about in a broader U.S. based population with higher prevalence of other cardiovascular risk factors?

And how about patients with more aggressive statin therapy and LDL control?

There remains an unmet medical need for patients with elevated triglyceride levels and other residual risk factors beyond statin controlled LDL, but we do not yet have therapies with proven cardiovascular benefit in these patients. REDUCE-IT was designed to test the benefit of high-dose icosapent ethyl in such high-risk patients.

With that, I will turn to my colleague, Dr. Bhatt, to walk us through the important REDUCE-IT results.

Applicant Presentation - Deepak Bhatt

DR. BHATT: Well, it's really a great privilege to be here and to be able to speak to all of you about the REDUCE-IT trial. By way of disclosure, I receive research funding from Amarin Pharma that goes to Brigham and Women's Hospital for my role as the study chair and principal investigator of REDUCE-IT.

You already heard a little bit about the

JELIS trial published in Lancet, and this is an important study by way of background. This was a trial of Japanese patients who were randomized to a statin alone or statin plus ethyl EPA at 1.8 grams a day, Epadel, in a so-called PROBE design, prospective, randomized, open-labeled with blinded endpoint adjudication; 18,645 patients in a randomized trial but open label, meaning that there is no placebo per se, just a control arm, reporting that there was a significant 19 percent relative risk reduction in these patients.

Of note, there was no prespecified minimum triglyceride requirement such that, at baseline, the average triglyceride level, prior to statin initiation, was only 154 milligrams per deciliter, and the on-study reduction in triglyceride levels was only 5 percent, as Dr. Miller alluded to. Some other key features of the trial population included that it was 80 percent primary prevention, 69 percent women, and that the LDL was managed in accordance with the Japanese guidelines at the time.

Epadel is a stable prescription form of EPA available in Japan and contains largely the same active ingredient as icosapent ethyl. Importantly, there was a consistent benefit reported in both the secondary prevention and primary prevention cohorts in this study. Of course, the event rate is lower in the primary prevention cohort, but there is no evidence of heterogeneity of the observed benefit.

REDUCE-IT is a multinational, randomized, double-blind, placebo-controlled trial. It evaluated icosapent ethyl 4 grams a day, in statin-treated patients with well-controlled LDL cholesterol, moderately elevated triglyceride levels, and cardiovascular risks. It was designed with an approximate sample size of 7,990 patients and followed up until approximately 1,612 events occurred, giving it 90 percent power. The primary endpoint was MACE, major adverse cardiac events.

I served as the study chair and global principal investigator for this trial. The steering committee consisted of academic experts in clinical trials and cardiovascular prevention,

including Dr. Christie Ballantyne, Dr. Mike Miller, and Dr. Eliot Brinton, all of whom are here today. The independent Data Monitoring Committee was chaired by Dr. Brian Olshansky, who is here today in the audience as well.

There was an independent statistical validation that was headed up by Professor Stuart Pocock. This was at the primary endpoint, the primary analyses, and the total event analyses that I'll be sharing with you in a little bit. Dr. Jane Lee and the Baim Clinical Research Institute in Boston also independently validated these analyses.

The independent Clinical Endpoint Committee, composed of cardiology and neurology experts and chaired by Dr. Michael Gibson, who's here today, and also represented by Dr. Bob Giugliano, who's here today, adjudicated the events blinded to the treatment assignment.

Here are the key inclusion criteria and exclusion criteria from REDUCE-IT it. Patients were on stabilized statin therapy for at least 4 weeks prior to randomization. Their triglyceride

levels were intended to be between 135 and 500. The inclusion criteria stated 150 to 500, but we allowed a 10 percent variance given the known variation of triglyceride levels; so 10 percent of 150 is 15; 150 minus 15 is 135.

That's how we ended up with the actual range of 135 to 500; though, in fact, when we analyzed not just the prerandomization qualifying triglycerides, but then also the day of randomization triglycerides, we saw that about 10 percent of the population randomized had baseline triglycerides between 100 and 150 milligrams per deciliter.

Part way through the trial, the majority of the steering committee recommended changing the entry triglycerides to 200 milligrams per deciliter, and this was based on the fact that we were enrolling very briskly in that cohort under 200 milligrams per deciliter, and therefore wanted to make sure that the trial, when it ended, had a broad representation of triglycerides, including those over 200.

So anyway, that's why we changed it, and that was the majority opinion of our steering committee to do so, though I've got to say personally I actually wanted to lower the triglyceride entry criteria because I thought there would likely be benefit at even lower levels. But anyway, we went with the majority opinion of the steering committee, and that's how we got to the 200.

So hopefully, this clears up why the protocol, the papers, and the actual range of triglycerides enrolled have slightly different numbers.

The LDL cholesterol is between 40 and 100 milligrams per deciliter. There were two cohorts, a secondary prevention cohort that consisted of patients with established cardiovascular disease. There was cerebrovascular disease. There was coronary artery disease or peripheral artery disease that could be part of that established cardiovascular disease, and those folks had to be at an age range greater than or

equal to 45 years.

There was also what I'll be referring to as a primary prevention cohort, but to be specific, that consisted of patients with diabetes, age greater than or equal to 50 years, with at least one additional risk factor for cardiovascular disease. Exclusion criteria included class 4 heart failure, severe liver disease, pancreatitis, fish or shellfish allergy, statin intolerance, or uncontrolled diabetes or hypertension.

The overall design is shown on this slide. Patients were screened. There was a lead-in phase where patients were stabilized on their statin dose. There was washout of medicines that could affect triglyceride levels, such as Omega-3 fatty acids, fibrates, niacin, and then patients were qualified for entry into the trial based on their lipids.

They were randomized in a 1-to-1 fashion to either 4 grams of icosapent ethyl or to a matching placebo and continued statin therapy, and then they were followed for a median of 4.9 years, or about 5

years you could say, and a maximum of 6.2 years for cardiovascular endpoints. The placebo that was chosen was pharmaceutical grade mineral oil. It was selected in conjunction with FDA input based on the need to match the color and consistency of icosapent ethyl.

The primary endpoint was time to first occurrence of the composite MACE, or major adverse cardiovascular events, consisting of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization. The key secondary endpoint was time to first occurrence of the composite of CV death, nonfatal M, or nonfatal stroke.

Secondary cardiovascular endpoints were tested with a predefined hierarchical testing sequence, and there were tertiary and exploratory endpoints that we also assessed such as sudden cardiac death and cardiac arrest. All endpoints were independently adjudicated, blinded to treatment assignment, including revascularization and unstable angina requiring hospitalization.

Now, let me share with you the efficacy results from REDUCE-IT. Shown here in the CONSORT diagram is the basic design of the study and its execution. We screened 19,212 patients and randomized 8,179. It's a pretty high proportion of those that were screened, 43 percent, who are ultimately randomized to either icosapent ethyl or to a matching placebo, and of those patients, vital status was known at the end of the trial in 99.8 percent.

Shown here are the baseline characteristics. The average age was 64. Approximately 30 percent were female; 10 percent were non-white; and 70 percent or so came from westernized regions. As far as the secondary prevention cohort as planned per study design. That was approximately 70 percent of the population, and approximately 30 percent were in our so-called primary prevention cohort. Exetimibe use was about 6 percent. The vast majority of patients were on moderate or high-intensity statins, and about 50 percent of the patients had type 2 diabetes.

The median hemoglobin A1c in those with diabetes was 7 percent. The average triglycerides were on 216 milligrams per deciliter at baseline, with an average HDL of 40 and an average LDL of 75. Approximately 10 percent of the patients had baseline triglycerides between 100 and 150 milligrams per deciliter.

The baseline medical therapy was excellent. Approximately 80 percent were on antiplatelet therapy; 20 percent were on dual antiplatelet therapy; and 10 percent were on anticoagulants; 78 percent were on ACE inhibitors, or ARBs; 71 percent were on beta blockers; and of course, by protocol, patients were to be on statin therapy.

Shown here is the primary endpoint of the trial, 5-point MACE, or major adverse cardiovascular events, consisting of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. This was reduced over an average of approximately 4.9 years from 28 percent to 23 percent, a hazard ratio of 0.75, a relative risk reduction of approximately 25

percent, an absolute risk reduction of approximately 5 percent, with a number needed to treat of only 21.

The key secondary endpoint of the trial was cardiovascular death, nonfatal MI or nonfatal stroke, and this, too, was reduced over an average of approximately 5 years from 20 percent to 16 percent, a hazard ratio of 0.74, a relative risk reduction of 26 percent, an absolute risk reduction of 4 percent, with a number needed to treat of only 28.

Shown here is our prespecified hierarchical endpoint testing. On the top row is the primary endpoint and then the key secondary endpoint that I just showed. Then there are a number of different composite and individual endpoints that were significantly reduced in the hierarchical testing sequence shown in green.

These included significant reductions in fatal or nonfatal MI, which was reduced by 31 percent; urgent or emergent revascularization, which was reduced by 35 percent; hospitalization

for unstable angina, which was reduced by 32 percent; fatal or nonfatal stroke, which was reduced by 28 percent; and death from cardiovascular causes as well, which was significantly reduced by 20 percent.

On the bottom is total mortality, where there was a trend to a 13 percent lower rate with a p-value of 0.09. I will note that the hazard ratio for non-CV mortality was 1.0, so there was no offsetting non-CV mortality risk to counterbalance the significant reduction in CV mortality.

Shown here is the primary endpoint in several different subgroups. As you can see, there is a very consistent benefit favoring icosapent ethyl versus placebo. This is true for the primary endpoint. This is also true for the secondary endpoint that I'll show in a moment. But let me first callout to you a few specific subgroups.

This here is the secondary endpoint, and let me, before moving to the subgroups, show you that. Again, it's a story of consistency across the board in terms of the subgroups that we examined. I'll

prespecify.

Now, let me move to the primary endpoint and start with CV risk categories. Here are the secondary and primary prevention cohorts showing general consistency of benefit; males and females, again, quite consistent, and those above or below age 65, where there may be some degree of differential benefit across groups, but nonetheless benefit in both groups. In those with diabetes and, importantly, those without diabetes also, a consistent benefit.

Triglycerides above or below 200 milligrams per deciliter at baseline, as well as above or below 150 milligrams per deciliter, consistent benefits. You'll recall that I mentioned about 10 percent of the population randomized had triglycerides below 150 milligrams per deciliter, and the benefits are very consistent in this subgroup; thus, generally consistent benefits across all these different subgroups and other ones, for the sake of time, that I haven't highlighted.

I will note the benefits were very consistent in both the 3,146 patients subgroup randomized from the United States and in the non-U.S. patients for the primary endpoint and the secondary endpoint. For that matter, for all the endpoints in the statistical hierarchy, and although a subgroup, reassuringly, icosapent ethyl achieved a significant 34 percent reduction in cardiovascular death and a significant 30 percent relative risk reduction in 2 percent -- or I should say 2.6 percent -- absolute risk reduction in all-cause mortality in the U.S. patients, as published earlier this week in Circulation.

A few tertiary endpoints I want to call your attention to, and these are prespecified endpoints, I should mention, adjudicated blinded to treatment assignment. Cardiac arrest was significantly reduced by about 50 percent, and sudden cardiac death was significantly reduced by about 30 percent.

I mentioned the significant reduction in revascularization a few slides ago. The decision

to revascularize is, in part, subject to the judgment of the treating physician. However, this is a prespecified endpoint adjudicated independently and blinded to treatment assignment in a placebo-controlled trial, so there should be no bias in the ascertainment of this endpoint or any determination of treatment effect. Coronary revascularization was significantly reduced, including significant reductions in emergent revascularization, urgent revascularization, and even elective revascularization.

What I've shown thus far are the data published in the New England Journal of medicine, the time-to-first-event analyses, the conventional way of analyzing data, the conservative way. Shown here is our analysis published in the Journal of the American College of Cardiology, not only of first events in green where I just showed the 25 percent relative risk reduction, but now also examining recurrent ischemic events where second events were significantly reduced, third events were significantly reduced, and fourth or more

ischemic events were significantly reduced, such that in examining the total ischemic events, there was a 30 percent reduction that was statistically significant.

Beyond the relative risk reduction, this depiction gives you a sense of the large absolute risk reductions provided by this therapy. Events were reduced in this population of 8,000 patients from 1500 with placebo to around a thousand with icosapent ethyl; so approximately 500 fewer cases of ischemic events in those patients randomized to icosapent ethyl.

This slide shows the data that I have already presented all in one slide, beginning with the primary endpoint and the 25 percent relative risk reduction in first events, and now also a 30 percent reduction in total events. This gives you a sense of the magnitude of benefit. Especially over time, you see that these curves are separating quite substantially, showing accrual of greater degrees of benefit with longer durations of therapy in these patients with atherosclerosis or are at

high risk for it.

Furthermore, it does show if you examine the placebo arm, here in red, that we have identified patients in this trial by virtue of the fact that despite dietary intervention, despite statins, they still have moderately elevated triglycerides, and these triglycerides are certainly a potent and reliable marker of risk, as well as a predictor of benefit from therapy with icosapent ethyl.

Here in the secondary prevention cohort, beginning with the time-to-first-event curves, and again adding the total event curves, you see the curves separating at about a year for first events, similar to what we're seen with statins in stable patients. Here in our primary prevention cohort, again, beginning with the time-to-first-event analyses, the curves separate a bit later at about two years or so for first events; again, similar to what was seen with statins as one moves down the risk ladder.

Now adding the total event curves, which provide a more comprehensive assessment of the

impact of icosapent ethyl in reducing the burden of events in patients initially enrolled into our primary prevention cohort, the event rates are, of course, lower here than in our secondary prevention cohort, but there is still clinically worthwhile benefit. It just takes a bit longer to emerge.

Let me now share with you some exploratory and some post hoc analyses, examining the effect of icosapent ethyl versus placebo across tertiles of baseline triglycerides. At the top of the slide is the time to first event for the primary composite endpoint, and at the bottom is the total events analysis, and it's really the same story in both cases; that is a consistency of benefit favoring icosapent ethyl versus placebo across these three triglyceride tertiles at baseline.

This certainly does suggest that there is more going on than just the triglyceride part of the story. But at any rate, across the full range of triglycerides that we enrolled in this trial, starting at around a hundred milligrams per deciliter, there is a consistent benefit.

REDUCE-IT was designed as a cardiovascular outcome trial. It was not a biomarker study, but of course we did examine a few different biomarkers, as shown on this slide, and there were significant changes in a number of biomarkers. But in particular, the biomarker that changed the most was the level of EPA, which went up by over 350 percent.

So while there certainly was a reduction in triglycerides, as was already established with this drug, at least in my opinion, what is really driving the benefits we see is this large increase in EPA. We gave icosapent ethyl. The EPA level went up by a lot, and I think that explains a variety of different benefits that we observed in the trial, as opposed to the relatively modest changes in triglycerides or the small changes in other biomarkers such as LDL or CRP.

Now interestingly, examining triglycerides on treatment at a year, we see that in those patients in the icosapent ethyl arms, in green and blue, who did, either, or didn't achieve

triglycerides above or below the 150 milligram per deciliter mark versus the placebo in red, a very consistent and similar degree of benefit, arguing once more that there's probably more going on to this drug's mechanism of action than just triglyceride reduction, but also importantly demonstrating that in this whole population of patients that we enrolled, across a broad range of triglycerides, both baseline levels and now one-year levels, a very consistent benefit is seen.

Now, I want to say a few things about the changes in LDL in this trial. First of all, they were not dissimilar to what's been seen in other contemporary cardiovascular outcome trials. Shown here is a variation in LDL in ORION, and the similar degree of LDL variation in REDUCE-IT; so really nothing unusual here with respect to LDL. In ODYSSEY OUTCOMES, where I was on the executive committee, as well, we saw a slight upward drift in LDL cluster on the placebo arm.

As you can see, what we've done here is examine the icosapent ethyl patients in blue, and

then in red are the placebo patients. Those placebo patients with an LDL increase in a year, and that's the dotted red line -- hopefully that projects -- are those with no change or decrease in LDL; that's the solid red line.

Again, it's a story of consistency; any way you slice the data, a consistent benefit. And while we are getting into the different data cuts, and one shouldn't necessarily demand p-values to be positive, we also see a significant benefit in each of these patient groups. What this tells me is that even in those patients who had LDLs that were decreasing in the placebo arm, icosapent ethyl is still superior.

Of note, per FDA request to the independent Data Monitoring Committee kept a careful eye on the placebo group and concluded that mineral oil was unlikely to be driving the beneficial effect of icosapent ethyl. The placebo group event rate was consistent with our initial projections and current cardiovascular outcome trials, and similar analyses conducted for other biomarkers beyond LDL showed

similar results as to what I've shared on this slide.

For example, the CRP story is the same. These results are really analogous to what I just showed you; now in red, the placebo group CRP increasing in the dotted red line and then not changing or decreasing in the solid red line. Again, hopefully all that projects well. In either case, a consistent benefit of icosapent ethyl versus placebo; even a significant benefit in these data cuts.

So these two slides really argue that any changes in LDL or CRP occurring in the placebo arm are relatively small in magnitude and aren't driving the substantial benefit that we saw in this trial.

Just to speak about the mineral oil placebo a little bit more, the sponsor, but also importantly the FDA, have conducted their own multiple analyses, exploring the possible effects of mineral oil on statin absorption, and none alter the study conclusions. The Amarin analyses show a

lack of evidence for a mineral oil effect. For example, the placebo event rate is consistent with comparable historical cardiovascular outcome trials, so it doesn't appear that anything funny was happening in the placebo arm.

As I mentioned before, the placebo LDL changes are consistent with lipid-lowering treatment studies. The LDL changes were also consistent with some degree of regression to the mean. There was no apparent effect of biomarker increases on placebo group outcomes, as I just reviewed. And in additional extensive analyses, I've not shown but all are contained in your briefing book if you're interested in the details, there was no clinical evidence of malabsorption, nor differential LDL, or outcome effects based on statin type or statin lipophilicity.

So we see no evidence of an effect, and any theoretical effect would be minimal. The largest LDL differential translates, per the FDA analyses, to a maximum possible impact of approximately 3.1 percent points of the observed 25 percent

relative risk reduction.

Finally, a prior but second trial supports the CV benefit of EPA therapy, including a 19 percent relative risk reduction in JELIS, using a lower dose of EPA in a population, a Japanese population, with higher baseline levels of EPA. And while typically considered a major limitation of JELIS in the context of this mineral discussion, it's actually a strength. JELIS reported a 19 percent relative risk reduction in a secondary and primary prevention population, in an open-label trial without a placebo

Rather than minor changes in LDL or CRP, or modest changes in triglycerides, what I think was really driving the benefits we saw in this trial was the change in EPA levels. In fact, we measured EPA levels at baseline, and at various points in the trial for that matter. Now, stability testing does not cover the storage times for samples used for these EPA analyses, I'll mention, but the findings may still be informative.

Tertiles of EPA shown on this slide are

1 based on year 1, 2, and 3, and last visit EPA
2 levels in icosapent ethyl, and compared with
3 placebo patients who had at least one post-baseline
4 EPA level. As you can see, the higher level of
5 achieved EPA, the higher the degree of benefit. So
6 as opposed to small changes in LDL, or CRP, or even
7 modest changes in triglycerides, the only analysis
8 we found that correlates biomarker changes with
9 outcomes is that free EPA, and that is likely the
10 mechanism of benefit. Now, I predict that it will
11 take years to sort out the exact mechanisms of the
12 benefit of the EPA, but the clinical efficacy data
13 are clear.
14 Thus, regarding the efficacy data, icosapent
15 ethyl 4 grams a day added to statin therapy reduced
16 the primary composite endpoint by 25 percent over
17 statin alone. There was substantial clinically
18 meaningful, statistically significant, and
19 consistent cardiovascular risk reduction that was
20 demonstrated. The key secondary endpoint was
21 reduced by 26 percent.
22 There were significant reductions across the

entire prespecified testing hierarchy. Each MACE component was substantially reduced. There were generally consistent reductions across multiple subgroups, and the total events for the primary composite endpoint were reduced by 30 percent

Let me now shift to review the safety findings from REDUCE-IT. Let me start, first, with the treatment emergent adverse events, or TEAEs, as I'll call it. The TEAE event rates represent the enrolled high cardiovascular risk patients and the 4.9-year median study follow-up, just in case we're comparing these rates with other trials. The important message here is that there was no overall difference in adverse events.

Shown here are the icosapent ethyl and placebo arms. And just to orient you, the top row is patients with at least one TEAE, and in the bottom row are patients with SAEs leading to death. The p-value for each of these rows is non-significant, but more importantly, the actual rates of events in these two arms are virtually identical.

This is true if we examine very sensitive definitions of adverse events in the top row or very specific definitions of adverse events in the bottom row. Regardless of how you look at it, overall, the 30,000-foot view is that this drug was tolerated as well as a placebo and was as safe as a placebo. On the flip side, overall, the mineral oil placebo was not causing any evident harm either.

Now, let me get into some more details about safety. To avoid duplicate counting, clinical events were counted in either safety or efficacy analysis, but not in both. Both are presented here, where separate analyses include related events.

The safety analysis that I'm going to mention first is for peripheral edema. It was the only TEAE that was greater than 6 percent and higher, and statistically significantly so, than placebo. But I'll point out that there was no increase in the rate of heart failure in the icosapent ethyl patients. In fact, the hazard

ratio was 0.95 for heart failure; 0.97 for heart failure requiring hospitalization.

The other two things I'll discuss in greater detail are bleeding and atrial fibrillation/flutter in the slides to follow. First, let me start with the adverse events of interest with respect to serious bleeding. If we look at all bleeding TEAEs, the rates were 11.8 percent and 9.9 percent, and this was a significant difference.

But now let's break that down into bleeding SAEs, and by SAEs, I'm meaning significant adverse events, of course. For more serious types of bleeding, that was increased from 2.1 percent to 2.7 percent with a p-value of 0.06, but no significant differences in gastrointestinal bleeding, central nervous system bleeding, other serious forms of bleeding, or intracranial bleeding. As well, hemorrhagic stroke, which was an adjudicated endpoint, was not significantly different.

What about fatal bleeding? Well, any

bleeding with a possible fatal association is shown on the top row, 0.6 percent versus 0.8 percent for icosapent ethyl placebo, with a p-value of 0.18, and likewise, no significant differences with respect to association with bleeding where it's likely contributing to a fatal event, 0.5 versus 0.6 percent; so overall, no signal for fatal bleeding.

As already noted, rates of all bleeding were higher in patients on icosapent ethyl overall, though statistically significant only in those on two or more antiplatelet agents at baseline, 14.3 percent versus 10.5 percent. As already noted, there was a trend towards higher rates of serious bleeding in the overall trial, but no significant differences in the categories of baseline antithrombotics shown here.

Perhaps more relevant for safety, shown here is all bleeding, but now in patients actually on antithrombotics at the time of bleeding as opposed to at baseline; that's what I just showed you. And here we see more bleeding in patients on one or two

antiplatelets, as well as on anticoagulants, though the absolute increases remain small, as with the prior baseline analyses.

Shown here is serious bleeding now in patients actually on antithrombotics at the time of bleeding; again, that's as opposed to baseline, though the message is essentially the same thing; rates that trend towards being slightly higher, though not quite statistically significant.

As someone who has done a number of antithrombotic trials through the years, I would say that there is a small increase in minor bleeding, but no significant excess in the forms of bleeding we worry about the most, such as gastrointestinal, intracranial, or fatal bleeding, including in those on dual antiplatelet therapy or on anticoagulants.

The increase in all bleeding was present in both the secondary and primary prevention cohorts with no significant increases in fatal or intracranial bleeding in either cohort. For serious bleeding, there is a trend towards an

increase in the secondary prevention cohort, but not in the primary prevention cohort, likely just reflecting the higher risk and greater use of background antithrombotics in the secondary prevention cohort.

Now, let me discuss atrial fibrillation or flutter requiring hospitalization for 24 hours or more. That was an adjudicated endpoint. All other atrial fibrillation flutter events reside in the safety database. You can see here that there was a significant increase in atrial fibrillation/flutter, adverse events from 4.5 percent to 5.8 percent. But as far as serious atrial fibrillation/flutter AEs, they were 0.5 and 0.5 percent; not significant.

As far as adjudicated atrial fibrillation/flutter requiring hospitalization, that was increased from 2.1 percent to 3.1 percent, and that was statistically significant. But importantly -- and I'll share the details with you in a moment -- the clinical consequences of atrial fibrillation in terms of stroke, MI, cardiac

arrest, sudden cardiac death, et cetera, Were reduced in the overall trial, as I shared with you earlier, and there were consistent results in those with a history of atrial fibrillation at baseline or who developed atrial fibrillation during the trial.

Here are the data for atrial fibrillation/flutter requiring hospitalization by whether patients did have atrial fibrillation or flutter at baseline by history or did not. As you can see from the bottom row, rates of hospitalization for new onset Afib or flutter were really very low, 2.2 percent versus 1.6 percent. So recurrent Afib in patients who already had a history of Afib was more common as opposed to de novo Afib.

This pattern extended into both the secondary prevention
and primary prevention cohorts. But importantly, if we look at those patients with a history of atrial fibrillation/flutter at baseline, yes/no now is shown here for this slide for the primary

composite endpoint, and for the key secondary composite endpoint, cardiovascular death, and all the different components of the primary endpoint that I've listed.

There is once more a consistency of benefit such that even in those patients with a history of atrial fibrillation or flutter at baseline, the drug performs as it did in other subgroups, a consistent benefit favoring icosapent ethyl over placebo.

What about patients who developed atrial fibrillation/flutter during the trial, yes or no? Again, it's the same story, a remarkable consistency of benefit favoring icosapent ethyl versus placebo, as with all the other subgroup analyses I've presented, as well as those I've not formally presented.

I would conclude, with respect to the safety, overall, icosapent ethyl was tolerated as well as placebo. Total bleeding events were increased with eicosapentaenoic icosapent ethyl, and serious bleeding trended toward an increase,

but serious bleeding event rates were low. And for the really worrisome types of bleeding like fatal bleeding, or intracranial bleeding, or GI bleeding, there weren't any significant differences between the two treatment arms.

A higher incidence of atrial fibrillation/flutter was observed with icosapent ethyl, but overall rates over the course of an average of 5 years were low, and consequences associated with atrial fibrillation/flutter were reduced in the full study cohort with consistent benefits in the Afib subgroup; and these were safety considerations that can be addressed within the labeling.

If we examine the benefits and risks of icosapent ethyl, we see the magnitude of beneficial reductions in cardiovascular events and the slight increases in serious bleeding or nuance at atrial fibrillation do not outweigh these benefits.

Let me now focus on our primary prevention cohort. Patients with diabetes and at least one additional cardiovascular risk factor -- that's

what I'm referring to -- as is common in trials with hybrid secondary and primary prevention populations, there are always some patients that end up in the so-called primary prevention cohort that may have had some sort of cardiovascular history, even if it did not meet the exact inclusion criteria of the trial. I remember this happened, to an extent, with CHARISMA and SAVER for example.

This slide represents removal of those patients in the primary prevention cohort that had some sort of cardiovascular history of sorts. And what we examined here, in response to the recently posed FDA questions to the panel, is our primary prevention cohort now stratified by the pooled cohort equation risk score, that is looking at the 10 year atherosclerotic cardiovascular disease risk, less than or greater than or equal to 10 percent.

So what happens by this demarcation of data? As you can see, there appears to be no benefit in those with a risk of less than 10 percent in this

primary prevention cohort, but in those with greater than or equal to 10 percent 10-year risk, there appear to be benefit. So there's a continuum of risk, and we believe we've identified a high-risk, primary prevention diabetes cohort who would benefit from icosapent ethyl as do the secondary prevention patients studied in this trial.

As well, examining now the benefit-risk profile in our primary prevention cohort, the benefits in those with a 10-year risk greater than or equal to 10 percent appear to outweigh the serious bleeding and nuance at Afib risks. Thus, we feel we have identified those patients who benefit from within our diabetes prevention cohort, so we think we have answered the question that was posed to us by the FDA for all of you to consider today.

To conclude, regarding the overall REDUCE-IT trial results, compared with placebo, icosapent ethyl 4 grams a day significantly reduced important cardiovascular events by 25 percent, including a 31

1 percent reduction in heart attack; a 28 percent
2 reduction in stroke; a 20 percent reduction in
3 death due to cardiovascular causes; and a 30
4 percent reduction in recurrent and total ischemic
5 events.
6 There was consistent efficacy demonstrated
7 across the prespecified testing hierarchy, as well
8 as other cardiovascular endpoints and across
9 multiple subgroups. The low rate of adverse events
10 is quite reassuring and can be addressed within
11 labeling. There was a small but significant
12 increase in atrial fibrillation or flutter, but as
13 I mentioned, consistent benefits even in those
14 subgroups. There was an increase in all bleeding
15 with a trend towards an increase in serious
16 bleeding, but no increase in the really bad forms
17 of bleeding like fatal or intracranial hemorrhage.
18 Thus, that leaves us with a very favorable
19 benefit-risk profile with generally consistent
20 effects across multiple subgroups, including a
21 secondary prevention and high-risk primary
22 prevention with diabetes, with 10-year

atherosclerotic cardiovascular disease risk greater than or equal to 10 percent, and across the full range of baseline triglycerides that we studied.

Finally, moving just beyond trial specifics, I would say as a practicing physician, I think the REDUCE-IT trial shows that icosapent ethyl is an extremely useful addition to our armamentarium for cardiovascular risk reduction across the continuum of secondary prevention and high-risk primary prevention. It's a drug that's easy to take, side effects that can be addressed in labeling, and it's generally as well tolerated as a placebo, with effect sizes that are quite substantial. And especially with longer durations of treatment, this form of therapy applied to the right patients could have a substantial impact on their overall atherosclerotic burden.

We've shown in REDUCE-IT, and external data sets now support, that even modestly elevated triglycerides in at-risk patients effectively identify patients at high risk for future ischemic events. Clinically, I see these patients coming in

with first and recurrent ischemic events all the time, and the fact that they appear initially stable is deceptive because with long enough follow-up, we see just how high their event rates are over time. Icosapent ethyl could put a major dent in these event rates and provide a new option for these currently at-risk patients.

Thank you very much for your attention. I really appreciate it. I know it was a lot of information, but I wanted to provide you with data that went beyond the primary publications and to address questions posed by the FDA to hopefully be useful to you in your decision making.

Let me now call up Professor Ann Marie Navar from Duke University, who's going to speak about the clinical implications of the REDUCE-IT trial. Thank you very much.

Applicant Presentation - Ann Marie Navar

DR. NAVAR: Thank you, Dr. Bhatt, and thank you to the panel.

I'm Ann Marie Navar. I'm a clinical cardiologist at Duke University and a researcher at

the Duke Clinical Research Institute. I'm here to share my perspectives on the clinical implications of the REDUCE-IT cardiovascular outcomes study. I have received funding from Amarin for epidemiologic studies to my institution, as well as personal consulting fees, including participation in advisory boards and scientific consulting.

Having been asked to give my clinical perspective, it's important for us to be reminded of the magnitude of the clinical challenge that we face in cardiovascular disease. We know the significant burden of cardiovascular disease in the United States. It's the leading cause of death for United States' adults, causes substantial morbidity, and increasingly higher costs to our healthcare system.

We know, based on epidemiologic data, including what was summarized by Dr. Miller, that adults with high triglycerides are at particularly high risk of cardiovascular disease, and as the rates of diabetes, obesity, and metabolic syndrome in the United States increase, we're also seeing

increases overall in the population's triglyceride levels.

Even with other secondary prevention therapies, we cannot eliminate the risk of cardiovascular disease events in patients in secondary prevention, and even with preventive therapies, we cannot prevent the development of incident cardiovascular disease in high-risk adults.

In REDUCE-IT, a population with well-controlled LDL levels, high rates of statin use, and high rates of effective antithrombotic agents, we still see an annual event rate of 5.7 percent with around 1 in 4 patients experiencing a cardiovascular event over the course of the study.

Clinically, when we see patients with high-risk conditions like diabetes, high cholesterol, or high blood pressure, we like to be able to have a treatment specific to that condition. Unfortunately, for the patients that we see with elevated triglycerides, we have no

FDA-approved therapy to target this population and help further lower their risk of cardiovascular events.

Our patients also want these therapies. Despite a lack of cardiovascular outcomes data, millions of adults with elevated triglycerides are on fibrates for which there are no cardiovascular outcomes data, and even more are on supplement doses of fish oil, where clinical trials have shown no benefit to therapy in terms of reducing cardiovascular events.

Overall, I am impressed with the robustness and consistency of the REDUCE-IT results and that the benefits of icosapent ethyl outweigh the risk in high-risk patients with elevated triglycerides. In the next few slides, I'll describe why icosapent ethyl will be an important addition to the armamentarium we have to prevent and treat cardiovascular disease.

Why will the findings of REDUCE-IT change my practice as I take care of patients in the clinic? Well, first and foremost, REDUCE-IT was a large,

global, randomized, placebo-controlled outcomes trial in over 8,000 patients that showed compelling data for a strong clinical benefit for cardiovascular risk reduction. The magnitude of benefit, a 25 percent relative risk reduction, is remarkable, and particular in comparison with other recently approved therapies targeting dyslipidemia and cardiovascular risks.

For example, PCSK9 inhibitors, which we now routinely use in clinical practice and are part of clinical guidelines, showed a relative risk reduction of 15 percent, albeit over a shorter time period. It is also reassuring that the relative risk reduction seen in the REDUCE-IT trial was consistent with what was reported in JELIS.

From a clinical perspective, the patients in REDUCE-IT look a lot like the patients with elevated triglycerides that we see in our day-to-day practice: on blood pressure therapies, on LDL-lowering medications, on appropriate secondary prevention with well-controlled LDLs, but still at risk for cardiovascular events.

Finally, REDUCE-IT found a substantial and consistent clinically meaningful result across a wide range of cardiovascular endpoints and subgroups. These data were shown in Dr. Bhatt's presentation. From my perspective, it is reassuring that we are not seeing results driven by one particular piece of the MACE composite that may be less clinically meaningful to our patients, like decreases in revascularization but not heart events like myocardial infarction or stroke. Rather, we see consistent reductions for all of the different pieces that contributed to the overall primary and secondary composite endpoints.

There were some risks that Dr. Bhatt showed that were associated with the use of icosapent ethyl compared with placebo. In general, the therapy was well tolerated, so this is a therapy I can expect my patients to stay on over time. This is an important feature for those in the primary prevention group, who we saw needed a longer duration of therapy to experience the largest clinical benefits.

There were two safety signals that stood out, bleeding and atrial fibrillation. I do not think that these offset the clinical benefit of icosapent ethyl, and I am confident that these signals can be communicated effectively to patients, and providers can manage these symptoms clinically.

As it relates to bleeding, there was an absolute increase in the rate of bleeding in the icosapent ethyl arm, but the risk was low with a 0.6 percent absolute increase in the rate of serious bleeding events over five years. This level is similar, if not lower, than what we have seen in a number of other therapies we use for cardiovascular prevention, including aspirin.

Also, most bleeding occurred in patients who were already on other antithrombotic therapies. These are patients for whom we are already monitoring for bleeding and who are already watching themselves for symptoms of bleeding, so I believe that this increased risk can be adequately detected and then managed in the clinical setting.

Importantly, while not statistically significant, there was actually an absolute decrease in the rate of fatal bleeding amongst those who were treated with icosapent ethyl compared with placebo, so the increase in bleeding does not offset the benefit with respect to MACE.

Atrial fibrillation and flutter, which I'll abbreviate to just say Afib, was the other safety signal that came out. First, it's important to point out that Afib is a condition that is highly prevalent in primary care cardiology and endocrinology practices; so prescribers of icosapent ethyl will be familiar with discussing Afib with their patients, as well as identifying and managing atrial fibrillation either themselves or through appropriate referrals.

Next, we need to note that atrial fibrillation and flutter were not systematically collected in this study, nor was it prospectively screened for. This was a prespecified component of a broader endpoint of cardiac arrhythmias. REDUCE-IT was not designed to comprehensively and

systematically assess the true incidence of all atrial fibrillation, which is often silent and goes undetected, so we really need to be careful to not overinterpret these findings.

The biggest risk increase in atrial fibrillation was observed in those who had a preexisting diagnosis of Afib. These patients should already be anticoagulated for stroke prevention, which does not change if they have more symptomatic events. So icosapent ethyl wouldn't alter these patients' risk of stroke or need for anticoagulation.

These patients may need changes to the rate or rhythm control strategies, but this is something we deal with in patients with atrial fibrillation all the time and does not affect the clinical benefit of reduced cardiovascular events, including myocardial infarction and stroke.

New onset atrial fibrillation on the other hand, or atrial fibrillation events in those who did not have a prior clinical history, is likely more clinically impactful, as these patients may

need new medications, including anticoagulation. However, the magnitude of increase in that particular group was quite low, a 0.6 percent absolute difference in adjudicated atrial fibrillation events in those without a history of atrial fibrillation or flutter compared with placebo.

With this small increase in mind, the most important piece of information as it relates to atrial fibrillation is then to look at the rate of stroke, which is the most feared complication of atrial fibrillation.

In REDUCE-IT, the risk of stroke was lower in those on icosapent ethyl compared with placebo, even despite the observed increase in atrial fibrillation events. Reassuringly, secondary analyses suggest that the development of atrial fibrillation did not affect the efficacy of icosapent ethyl in reducing the MACE composite or components of the MACE composite. Also, the more dangerous ventricular arrhythmias, including cardiac arrest and sudden cardiac death, were both

reduced in the icosapent ethyl arm compared with placebo.

While we don't want to scare patients away from therapy by overemphasizing bleeding and atrial fibrillation risks when there remains a favorable net benefit, clinicians should be able to communicate the risks and benefits of icosapent ethyl therapy to their patients as part of a standard risk-benefit conversation. It is true that atrial fibrillation and bleeding events are not desired outcomes for any of our patients, but we must keep in mind that neither are strokes, heart attacks, or cardiovascular death.

To put this back into context, I want to re-highlight the number of events avoidable with icosapent ethyl. These are data that Dr. Bhatt showed us that for every 1,000 patients treated with icosapent ethyl, we can prevent 159 events, including 76 revascularization procedures, 42 heart attacks, 14 strokes, and 12 deaths. All of these are events that are highly significant to our patients. This means that we're averaging 1 event

avoided for 6 patients treated over a 5-year period.

Given the risks we've seen and the difference in benefits presented in the different subgroups, though, how do we maximize the risk-benefit equation for our patients; and in particular, our patients in the primary prevention cohort?

First, it is true that the magnitude of benefit in the primary prevention population was lower than what was seen in the secondary prevention population. This slide shows the Kaplan-Meier curves for each of the cohorts, where the relative risk reduction for total events was 16 percent in the high-risk primary prevention cohort with diabetes and 35 percent in the secondary prevention cohort. This is not surprising, given that the event rate was lower in the primary prevention group compared with those in secondary prevention.

The other thing to recognize from these curves, which Dr. Bhatt also pointed out, is the

timing of separation of these curves. Unlike in secondary prevention on your left, where the curves separate quickly, we see a delay for curves to separate in primary prevention. Similar findings have been seen in other primary prevention studies, including for statins. It takes time to develop the complex atherosclerotic lesions that then go on to turn into events, so it takes time for a benefit to emerge.

But besides time on treatment, there is another way that we've now seen to maximize the benefit of treatment in the primary prevention group, and that's by focusing on the highest risk subgroups. This is important because the absolute benefit of treatment is driven by the absolute risk of events in the groups treated. We know clinically that not all patients with diabetes are the same. REDUCE-IT defined high-risk patients with diabetes by including not just a triglyceride and age cutoff, but also requiring the presence of other high-risk conditions.

Importantly, many of these factors occur

together, and in REDUCE-IT, 89 percent of those in the diabetes cohort had at least two or more additional risk factors. Yet, even within this high-risk REDUCE-IT population, defined by risk factors and elevated triglycerides, we still see heterogeneity in cardiovascular risks within the group.

These are the data that Dr. Bhatt on how stratifying primary prevention patients by baseline predicted 10-year ASCVD risk score as calculated by the pooled cohort equations. Here, we see three things. First, while this risk score wasn't developed specifically and only for patients with diabetes or patients who have taken statins, it actually did identify a subgroup of patients who had elevated cardiovascular risk.

The placebo event rate in the group with a predicted realistic less than 10 percent was 3.3 percent, and the placebo event rate in a group with a predicted risks over 10 percent was much higher at 13.2 percent; so we see that this risk score is reasonably stratifying risk within this

population.

Next, we observed that as the event rate increased, so, too, did the benefit of treatment. While in the overall population of primary prevention patients, the number needed to treat was 96, the NNT drops to 36 when limited to those who have a predicted ASCVD risk of 10 percent or more. And finally, while the benefit on MACE increased as pooled cohort score increased, we did not see a corresponding increase in the risk of bleeding and atrial fibrillation.

So the take-home point for me is that as cardiovascular risk increases in patients with diabetes, so overall does the benefit of therapy, and the risk-benefit equation becomes much more compelling when we focus on those with the highest risk.

In clinical practice, clinicians are already used to thinking about using predicted cardiovascular risk to guide therapy in primary prevention. Current American College of Cardiology and American Heart Association guidelines already

use the pooled cohort equation's 10-year ASCVD risk score to stratify adults with and without diabetes for both guiding statin therapy, statin intensity, as well as when to initiate pharmacologic therapy for blood pressure.

This score can be calculated easily with readably available clinical features, is available online, and, in fact, most electronic health records allow auto calculation of a patient's risk score right at the point of care. I am confident that using something like a 10-year risk score to help guide therapy for icosapent ethyl can easily be incorporated into clinical practice because it's something that we're already doing.

The favorable risk-benefit profile observed in REDUCE-IT in both secondary prevention and high-risk primary prevention patients with diabetes has already been recognized by multiple medical societies, which is shown on this slide. This includes The American Diabetes Association; the American Heart Association; the European Atherosclerosis Society; European Society for

Cardiology; and the National Lipid Association, with analyses from ICER showing icosapent ethyl is cost effective for cardiovascular risk reduction.

Shown on this slide is the specific criteria for whom these societies recommend use of icosapent ethyl, and I'll point out that this includes a combination of both high-risk primary and secondary prevention patients with elevated triglycerides defined as a level of greater than or equal to 135 milligrams per deciliter.

I applaud the sponsor for running the REDUCE-IT study to completion, and I hope that in reviewing the safety and efficacy of icosapent ethyl, that we keep in mind the high risk of the patients that were studied, the multiple concomitant therapies being used to treat these patients, and the long length of study of REDUCE-IT. The nearly 5 years of patient treatment in the trial adds to my confidence that the safety profile of this drug is exceeded by its clinical benefit.

We know there is an unmet need for further cardiovascular risk reduction in patients with

elevated triglycerides who are at high risk for cardiovascular events. Icosapent ethyl was well tolerated, and the safety signals that were observed can be communicated with patients and addressed in routine clinical practice.

The efficacy of icosapent ethyl was robust across a multitude of clinical endpoints, providing strong evidence that this is an important therapy to help lower cardiovascular risk in our patients. Personally, I see patients in clinic all the time with high triglycerides that remain at increased risk of cardiovascular events, many of whom ask me, "Doc, what more can I do to lower my risk of heart attack?"

For many of these patients, there is only so much that I can do, and they remain at elevated risks. I hope that with prompt approval of icosapent ethyl that I will have improved ability to offer this therapy to my patients immediately to start to further reduce their risk of important cardiovascular events. Thank you again. I will turn it back over to Dr. Juliano to conclude.

Applicant Presentation - Rebecca Juliano

DR. JULIANO: Thank you, Dr. Navar.

I'll provide just a few closing comments now, and then we can look forward to the committee's questions.

To reiterate the key points from today's presentation, REDUCE-IT was a large multinational, randomized, double-blind, placebo-controlled study of over 8,000 patients in 11 countries, with a median follow-up time of 4.9 years. It was designed and conducted under a special protocol assessment agreement. Patients were well managed with current therapies, including statin control of LDL cholesterol.

There was limited missing data for the primary analyses, and a final vital status was obtained for 99.8 percent of enrolled patients. There were consistent findings that were statistically and clinically persuasive within the primary composite, expanded MACE endpoint and within the key secondary hard MACE endpoint, and across the prespecified testing hierarchy of

secondary endpoints, except for the final endpoint of total mortality.

Each individual component of the primary and key secondary endpoints contributed to the overall efficacy demonstrated within these composite endpoints. There were generally consistent findings across subgroups and continued consistency of benefits suggested in the tertiary and exploratory cardiovascular endpoints.

Icosapent ethyl was well tolerated with limited safety signals. Overall, adverse events and serious adverse events were similar between the two treatment groups. Safety findings of bleeding and atrial fibrillation or flutter can be addressed within labeling to support clinician and patient decision making.

In regard to the FDA discussion topics for today, first, REDUCE-IT demonstrated clinically meaningful, statistically significant reductions in the primary expanded MACE endpoint and in the key secondary hard MACE endpoint. Amarin and FDA conducted multiple analyses, exploring the effects

of mineral oil on absorption, and none of these analyses alter the overall REDUCE-IT study conclusions.

Efficacy results were consistent across cardiovascular endpoints and generally consistent across subgroups. Each component of the primary composite endpoint contributed to the overall observed benefit, and each component also achieved statistical significance as an independent endpoint. Regarding safety, again, the bleeding and atrial fibrillation or flutter findings can be addressed in labeling in order to support appropriate patient/clinician discussions.

A favorable benefit-risk profile remains generally compelling across subgroups, including in the secondary prevention patients and in high-risk primary prevention patients with diabetes and other risk factors, in particular with a 10-year ASCVD risk score of 10 percent or greater.

REDUCE-IT provides sufficient efficacy and safety data to support a cardiovascular risk reduction indication for icosapent ethyl. Amarin

1 looks forward to labeling discussions with FDA
2 toward the goal of final label language and content
3 that reflect the REDUCE-IT study results.
4 Just a few final comments. Dr. Miller
5 walked us through the unmet need for the treatment
6 option to address the cardiovascular risk in
7 patients with persistently elevated triglycerides
8 despite statin stabilization; Dr. Bhatt walked
9 through the efficacy and safety results from the
10 REDUCE-IT study; and Dr. Navar walked through the
11 favorable benefit-risk profile in the high-risk
12 patients enrolled in REDUCE-IT.
13 We do want to take the opportunity to thank
14 the clinical investigators for the REDUCE-IT study,
15 and in particular, we thank the 8,179 patients
16 enrolled in the REDUCE-IT study. Some of these
17 patients were on therapy for up to 6.2 years, and
18 we're incredibly grateful for the commitment of
19 their time and their lives to the study.
20 We also thank the FDA for their
21 collaboration across what's been essentially a
22 decade-long design and conduct of the REDUCE-IT

study. With an expanded indication, we really do look forward to supporting healthcare decision makers in translating the REDUCE-IT research results into accessible and cost-effective therapy for the appropriate patients in need. With that, I thank all of you for your attention, and we look forward to your questions.

DR. BURMAN: Thank you all very much. Before we proceed with questions to the sponsor, I want to welcome Ms. McCollister-Slipp. Please introduce yourself.

MS. McCOLLISTER-SLIPP: Hi. I'm Anna McCollister-Slipp. I'm the consumer representative.

Clarifying Questions to Applicant

DR. BURMAN: Thank you very much.

We want to have clarifying questions to the applicant. Raise your hand or let Jay know what you'd like to say and when you want to say it. I know sometimes when people are on the phone on the committee, it's difficult to ask questions, so I wanted to ask Dr. Posner first.

Dr. Posner, do you have any specific questions for the sponsor?

DR. POSNER: Yes. Can you hear me?

DR. BURMAN: It was a little blurry, but I thought I heard you to say no. So if that's correct --

DR. POSNER: No. I said yes.

DR. BURMAN: Oh, he said yes? Okay.

(Laughter.)

DR. BURMAN: Thank you. Then we will proceed.

Please, we're happy to have your questions.

DR. POSNER: As someone who treats atrial fibrillation, I was a little bit confused by the data. I know there are [indiscernible - audio unclear] or major adverse effects, specifically. The question I have, mechanistically to physiologists, is atrial fibrillation causes many of these problems, besides bleeding, remodeling [indiscernible] of the heart. [Indiscernible - inaudible].

The question I have, are the MACE composites

taking into effect the chronic effects of [indiscernible] coronary artery disease?

DR. JULIANO: I'll see if I can reiterate that appropriately. I think the question is essentially whether or not we look specifically at whether the Afib or Aflutter caused remodeling, and therefore had a differential effect on potential endpoints.

If we could go back to the core presentation, Dr. Bhatt's, the efficacy with patients with or without Afib or Aflutter. We did not look specifically at cases of remodeling. I think I'll call up this slide, and then maybe I'll have Dr. Bhatt come up and give his perspective on whether or not there may be remodeling.

If I could have slide 1 up, please. As Dr. Bhatt showed in his presentation, these are patients that experienced atrial fibrillation or flutter while on study or who did not. Essentially, it's similar to the patients who came into the study with a history of Afib or Aflutter. What you see is in the primary composite endpoint,

the key secondary endpoint, in each of the components fitting into those endpoints, there's essentially a sign of benefit.

Now, what the mechanistic effect could be for the cause of Afib or Aflutter, we don't know. There actually was some literature prior to the study to suggest there could be an anti-arrhythmic effect of Omega-3 fatty acids; so there's some hypotheses out there about changes in electrolyte channels and such, but frankly it's very early literature. And again, the early literature suggested a benefit, and we're seeing the opposite here.

As far as any possible remodeling, we didn't look at that specifically, but, Dr. Bhatt, I don't know if you'd like to add your perspective on how that could be affected.

DR. BHATT: Sure. Thank you for the question. Perhaps we can just bring up, from the core deck, the slide that shows the new onset versus recurrent Afib hospitalization. If I heard the question correctly -- yes, please put up slide

1 that I'm seeing here.

If I heard the question correctly, and I'm sorry if I didn't, it had to do with atrial remodeling, but we didn't specifically examine that. What I will point out, though, is that the bulk of atrial fibrillation that was seen here was in patients that already had a history of it. In terms of new onset or de novo atrial fibrillation, as depicted on this slide, those rates were really quite low, 1.6 versus 2.2 percent, and that wasn't statistically significant, even.

More importantly, though, from a patient's perspective, the thing that patients worry about most, and doctors caring for patients who either have Afib or develop it as stroke -- and it really was good to see in the overall trial, there was no increase in stroke; in fact, a 28 percent reduction in stroke.

As well, if you can pull up, now, all the endpoints for atrial fibrillation by baseline, the yes/no slide, you'll see here as well -- please put up slide 1 -- even in the subgroup of patients with

a history of atrial fibrillation/flutter, if you look at the rates of nonfatal stroke, really quite favorable in terms of the hazard ratio. That's in the middle of this slide there, 2.1 versus 2.9 percent overall in the trial, and then 4.1 versus 6.3 in that subgroup with Afib at baseline.

So what we see in the overall trial and the subgroups that I presented early on in my talk, we're seeing in the patients, either with Afib at baseline or who developed during the trial, similar sorts of benefits. In particular, in terms of the patients that already have Afib, presumably their physicians are already doing what's needed for atrial fibrillation. So it's really the nuance at Afib one needs to consider, and that rate is quite low here. And again, even those patients seem to benefit from being on icosapent ethyl.

DR. BURMAN: Thank you. Dr. de Lemos? And let me remind everyone that we are going to take a break at 10:05. There's already a lot of questions. We probably will be able to take some of them later early in the afternoon. Please be as

succinct as you can, but we do want substantive questions and answers.

DR. DE LEMOS: James de Lemos. I'd like to see -- and this may take until after the break -- some math on the primary prevention cohort. The numbers aren't exactly adding up, to me, when you look at the subgroups presented initially by Dr. Bhatt; and when you all present your net analysis, the numbers don't add up.

By my math, I see 17 fewer primary endpoint events in the treatment group, in the eicosapentaenoic acid group in the CVR-2, that are balanced by 18 Afib events and 27 bleeds. But I'd like to see that data put together so that we can balance the very small absolute event reduction in the primary prevention cohort versus the adverse effects. I'd like to see all the bleeding, not just the major bleeding, and I'd like to see all the Afib events and not just the narrow definition.

DR. JULIANO: Okay. We'll have to see if we can pull that all into a central location. I know it's not quite asking for everything that you said,

but if we could have the ASCVD risk score above and below 10 percent. We did try to look at this by a couple of different manners.

Could I have the one with the primary endpoint as well as the serious bleeding and new onset Afib, please? Slide 1 up, please. As was shown in Dr. Bhatt and Dr. Navar's presentations, this does focus on the adjudicated new onset atrial fibrillation or flutter. It does focus on serious bleeding and, of course, the primary composite endpoint, but importantly, looking at patients cut with a risk score above or below 10.

I understand that this isn't exactly what you're asking for. We can look for a similar analysis for you, numbers-wise, that has a more, fuller data set.

DR. BURMAN: Thank you. We'll ask you for that later, if you would.

Dr. Konstam?

DR. KONSTAM: Yes. Just a quick follow-up on that. I think what would be best is a real demonstration of net clinical benefit, comparing on

one slide the absolute risk difference, not the hazard ratio of difference, because that's really how you figure out net clinical benefit.

I have three questions. I'd like to state them, and I don't know if we're going to get through the answer to all of them. The first is on slide 45, and this is for Dr. Bhatt, I guess. You can't really read any of this, but the third from the bottom caught my eye, so I blew it up on my computer. It turns out that it is baseline statin intensity with the lowest statin dose being the bottom line.

Now, I recognize that the number of patients in that group are small, and the number of events are small; therefore, you have the wide confidence intervals.

DR. JULIANO: Could I interrupt for one second? Could we have slide 2 up, please? We do have a callout of that --

DR. KONSTAM: Okay.

DR. JULIANO: -- group. It will make it a little bit easier.

DR. KONSTAM: Okay. Did see this earlier? I don't remember.

DR. JULIANO: The specific callout wasn't in the main presentation.

DR. KONSTAM: Okay. There it is. The patients' are small; the confidence intervals are wide. The interaction term is 0.12, which doesn't reach statistical significance. I think this is potentially important because the question is does the drug have the effect in patients who are not receiving statins, where many patients can't tolerate statins.

So if you would clarify, the low I believe is equivalent to less than 10 milligrams of atorvastatin. So if you're on 10 milligrams, you wouldn't be in the low group; is that correct?

DR. JULIANO: I believe that's correct. We can call up the explicit --

DR. KONSTAM: Yes. But the point -- I think a question that will come later -- is do these results apply to patients who are not on statin? And if not, the question is, well, why is it

showing up that way, and it related all to the absorption of statin issue?

DR. JULIANO: If I might, I could address that quickly or would you prefer to get all of your questions?

DR. BURMAN: No. Please address that.

DR. JULIANO: Okay. Two pieces. You do know that only 6 percent of the patients approximately fell within this patient cohort. The sample size is small. The confidence intervals are quite wide.

If I could have the JELIS study, overall study results? I think while we did not enroll a large proportion of patients with low-intensity statin and within REDUCE-IT, we're somewhat limited in how much we can speak to that patient population.

Slide 1 up, please. It's probably important to remember that in JELIS, actually, one of the major criticisms of the JELIS study design is that these patients were treated according to the current Japanese guidelines at the time, which

administered quite low doses of statins.

So essentially, the vast majority of these patients were all on low-dose statin therapy. Yet still, an achievement of a plasma level of EPA that's nearly identical to that achieved in a more westernized population with 4 grams per day had a substantial cardiovascular benefit.

So we just don't have the data within REDUCE-IT to look at patients on low-intensity statin. These were high-risk patients. The vast majority were on moderate- or high-intensity statin. But the cross-study comparison with JELIS gives us some comfort that there appears to be benefit when you do have a large population with low-intensity statin.

DR. KONSTAM: Okay. The second thing is, if I understand it correctly, hemorrhagic stroke does not appear in your adverse event totals because it's part of the efficacy endpoint. Is that correct?

DR. JULIANO: It was a prespecified endpoint that was adjudicated.

DR. KONSTAM: Right, and therefore, it does not appear in the safety data that you guys presented --

DR. JULIANO: But I do believe we presented --

DR. KONSTAM: -- in terms of --

(Crosstalk.)

DR. JULIANO: -- them. Yes. We have put them together, though. If I could have slide 1 up, please?

DR. KONSTAM: Yes. Because as I recall, the hemorrhagic stroke actually was higher in the active drug group.

DR. JULIANO: It was numerically higher, although very low in counts; so 13 occurrences in the icosapent ethyl arm versus 10 in the placebo arm. So you're right. It was a prespecified adjudicated endpoint, so it did not reside in the safety data set; it resided in the efficacy data set. The small numbers don't show a substantial difference.

DR. KONSTAM: Finally, if you could put up

slide 107. You guys have to correct me if I'm wrong, but the whole idea of the risk score -- and please clarify for me -- is based on the fact that for statins, the hazard ratio remains pretty constant throughout the level of risk. What changes is the absolute rate of events, and therefore the absolute risk reduction. Therefore, despite the hazard being reduced in a low-risk patient, you have a very minor effect on absolute events.

Here, what you have is different from that, I think, in that you actually have a hazard ratio difference in the two groups, which is different, and wouldn't it suggest to you that there is something different in the way the drug is acting in the two? It's not a function of absolute rates.

You follow me?

DR. JULIANO: Well, shown here are the absolute risk differences. So for the patients with a risk score of 10 percent or greater, there is a 4.21 percent absolute risk difference. I do believe that you're correct, that the higher the

risk, it's going to drive the more potential benefit.

DR. KONSTAM: I'm sorry. Then I misread the slide. That's great. Do you have a similar slide with the hazard ratios?

DR. JULIANO: I don't know if we have that available at this moment, but we could get you the hazard ratios if we don't.

DR. KONSTAM: Okay. Thank you. I misread the slide.

DR. BURMAN: That will be great. Just for clarification for me, and maybe the panel, in regard to your first question, you implied, or inferred, that some patients were not on statins. But really, on the study, if I remember the slide right, 99.4 percent --

DR. KONSTAM: Yes. Let me clarify. This is what I meant. If I remember correctly, the low category, I think in terms of atorvastatin dose, is less than 10 milligrams, so it's a very, very low dose of statin. So I'm sort of putting it in that group of low statin/no statin. And I think it's

1 going to be important in terms of where does the
2 drug apply, but it also really re-tweaks the
3 question of is the placebo affecting statin
4 absorption because the patients with the very low
5 statin dose, you'd think that any issue, absorption
6 would not apply. And in that group, in fact, there
7 was no benefit of the drug, albeit wide confidence
8 intervals.
9 DR. BURMAN: Thank you. Thank you for the
10 clarification.
11 We have multiple more questions. The
12 problem is we want to hear the FDA's presentation
13 after the break. But at 2:00, we will spend the
14 time, for the first part of the discussion,
15 revisiting some of these questions, so we do want
16 to get to them.
17 At the moment, we'll take a 15-minute break.
18 Panel members, please remember there should be no
19 discussion of the meeting topic during the break
20 among yourselves or any member of the audience. We
21 will resume at 10:20.
22 (Whereupon, at 10:07 a.m., a recess was

taken.)

DR. BURMAN: Welcome back. We will now begin with the FDA presentation.

FDA Presentation - Iffat Chowdhury

DR. CHOWDHURY: Good morning. My name is Iffat Nasrin Chowdhury, and I am the FDA clinical reviewer for this application. In this part of the presentation, I will discuss the REDUCE-IT trial design and conduct, as well as discuss the baseline demographics and patient characteristics.

REDUCE-IT was a randomized, double-blind, placebo-controlled, cardiovascular outcomes trial of 8,179 patients either with established cardiovascular disease or with diabetes, and at least one additional risk factor for cardiovascular disease. This trial was conducted to evaluate the clinical benefit of AMR101 versus placebo. The objective was to reduce the risk of the primary composite endpoint of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and unstable angina requiring hospitalization.

REDUCE-IT was initiated on November 21, 2011

and completed on May 31, 2018. Patients were enrolled from 11 countries, and approximately 39 percent of patients were from the U.S. Patients were randomized 1-to-1 to either AMR101 or placebo and stratified by CVD category, use of ezetimibe, and geographical region.

The study procedures were as follows. The screening period was approximately one month long and included statin stabilization, medication washout, and lipid qualification. After randomization, patient visits were conducted at month 4, 12, and then annually. All patients were to complete an end-of-study visit. This was an event-driven trial and planned to accrue 1612 efficacy endpoints, and there were two planned interim analyses at 60 percent and 80 percent of event adjudication.

Overall, trial conduct affirmed the integrity of the reported data. There was no evidence of shared unblinded data on review of notes from the DMC and Steering Committee. Also, review of some adjudication packages did not reveal

issues with incomplete ascertainment of events or ascertainment bias favoring either trial arm. There was reasonable alignment between investigators and the CEC for adjudicated events.

The triglyceride inclusion criterion was a value greater than or equal to 200 milligrams per deciliter, but less than 500 milligrams per deciliter. The original protocol allowed triglyceride levels greater than or equal to 135 milligrams per deciliter, but this was modified to increase enrollment of patients with higher TG levels in May 2013.

The LDL-C entry criterion was valued between 40 and 100, while on statin therapy with or without ezetimibe. Enrolled patients had either established CV disease, risk category 1, or diabetes and at least one other risk factor for CVD, risk category 2.

Those patients who were in CV risk category 1 made up approximately 70 percent of the total population of the study and included men and women greater than or equal to 45 years of age with

1 documented coronary cerebrovascular or peripheral
2 artery disease. Those patients in CV risk category
3 2 made up approximately 30 percent of the trial
4 population and were men and women who were greater
5 than or equal to 50 years of age, and had diabetes
6 and at least one additional risk factor for CVD,
7 which could be any of the following as listed on
8 the next slide.
9 These included risk factors such as men
10 greater than or equal to 55 years of age; women
11 greater than or equal to 65 years of age; smoking;
12 hypertension; microvascular complications of
13 diabetes; and the other criteria as listed.
14 Notable exclusion criteria included severe heart
15 failure; active severe liver disease; hemoglobin
16 A1c greater than 10 percent at screening; poorly
17 controlled hypertension; and creatinine clearance
18 less than 30 milliliters per minute or use of
19 dialysis. Excluded medications were
20 triglyceride-lowering agents such as niacin,
21 fibrates, and any Omega-3 fatty acid medication or
22 supplement. Other excluded medications were bile

acid sequestrants and PCSK9 inhibitors.

Regarding baseline characteristics of the trial, there were no important differences in demographic characteristics between the two arms. Of the 8,179 patients randomized into the study, the mean age was 63.4 years; 71 percent were men, 90 percent were Caucasian, approximately 59 percent had diabetes, and 92 percent had metabolic syndrome. Baseline lipids and C-reactive protein were similar between arms. The median LDL-C was 75 milligrams per deciliter and the median triglyceride was 217 milligrams per deciliter.

This slide further characterizes the TG profile of patients in the REDUCE-IT trial. Please note that although the trial included some patients with normal TG levels, approximately 90 percent of patients had TG greater than or equal to one 150 milligrams per deciliter, and 61 percent had TG greater than or equal to 200 milligrams per deciliter.

This slide shows patient disposition. Approximately 84 percent of patients on AMR101 and

82 percent of patients on placebo completed the study. 6.5 percent of patients on AMR101 and 7.2 percent of patients on placebo died during the course of the trial. Approximately 10 percent of patients on AMR101 and 11 percent of patients on placebo did not complete the study.

Patients who completed the study but were off study drug for greater than 30 days were described as off drug in study, ODIS. Patients who were ODIS at the final visit, final ODIS, were comprised of 22 percent of patients on AMR101, and 26 percent of patients on placebo. Vital status was known in 8,160 patients overall, 4,083 in AMR101 and 4,077 on placebo.

This slide summarizes the baseline characteristics of patients in the two CV risk cohorts. There was greater representation of women and nonwhite patients in risk category 2. Risk category 2 was made up almost entirely of patients with diabetes, while approximately 41 percent of patients in risk category 1 had diabetes. Both groups had a high incidence of patients with

history of hypertension or taking antihypertensives.

As expected, there were higher incidences of MI, stroke, and carotid revascularizations in risk cohort 1, the established CVD cohort. However, note in risk category 2, the number of patients with medical history, consistent with established CVD, was not insignificant.

Although it is important to note that the categories are not mutually exclusive, approximately 5 percent of patients in risk cohort 2 had a history of MI and about 5 percent had a history of stroke. Additionally, over 7 percent had a history of prior PCI and about 3 percent had a history of CABG. As expected, there were higher incidences of patients with diabetic microvascular complications in risk cohort 2, the diabetes cohort.

The majority of patients were on moderate to high intensity statins; 95 percent in risk cohort 1 and 88 percent on risk cohort 2. Baseline characteristics for risk category 2 suggest that

the trial population was at slightly higher baseline risk than the population strictly defined by the inclusion criteria.

Because approximately 95 percent had hypertension or were taking antihypertensive medications, and approximately 68 percent met age criteria for an additional risk factor, the majority of patients in this cohort had diabetes plus two or more risk factors for CVD. Furthermore, about 92 percent of patients in this cohort had TG greater than or equal to 150 and 57 percent had TG levels greater than or equal to 200 milligrams per deciliter despite being on moderate- to high-intensity statins.

Taken together, the baseline characteristics of risk category 2 define the higher risk population than the applicant's proposed indication. It would be challenging to extrapolate the results of the trial to patients without established CVD or diabetes on low-intensity statins with triglyceride levels greater than or equal to 135 but within the normal range.

I will stop here, and the FDA statistical reviewer, Dr. Roberto Crackel, will continue on to discuss the statistical analyses of the major efficacy findings.

FDA Presentation - Roberto Crackel

DR. CRACKEL: Good morning. I'm Dr. Roberto Crackel, the statistical reviewer from the FDA. I will present an overview on the statistical assessment of AMR101 efficacy in the REDUCE-IT trial. In this presentation, I will first give a brief overview of the trial, followed by the efficacy analyses and results. Dr. Yunzhao Ren will present his clinical pharmacology assessments of LDL-C increase in placebo patients and potential mechanism. I'll then discuss an indirect comparison with inert placebo. Finally, I will give my concluding remarks.

The REDUCE-IT trial was a double-blind, placebo-controlled trial. A total of 8,179 patients were randomized in a 1-to-1 fashion to either AMR101 or placebo. There are three stratification factors: CV risk category, use of

ezetimibe, and geographical region. The study duration was 6.5 years and the medium follow-up was 4.9 years. There are two interim analyses occurring at 60 percent and 80 percent of the planned final number of events.

I'll now discuss efficacy analyses and results. The primary endpoint was time from randomization to the first occurrence of any of the following: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina. After the primary endpoint achieved statistical significance, the following secondary endpoints were tested sequentially, starting with 3-point MACE, which is a composite of CV death, nonfatal MI, and nonfatal stroke.

The analysis population for the primary analysis was all randomized patients. The analysis model was the Cox proportional hazards model, which included treatment as an explanatory variable and geographical region, CV risk category, and use of ezetimibe as stratification factors. Time to first occurrence of MACE were censored at the time of

non-CV deaths. Patients who died with an adjudicated undetermined cause of death and without a proceeding endpoint event were included as events in the primary analysis. A two-sided alpha was adjusted to .0437 after the interim analyses.

Here are the primary endpoint results. The hazard ratio of AMR101 compared to placebo is 0.752, and the upper bound of the 95 percent confidence interval is 0.83. The p-value computed from the logrank test was less than 0.0001. There was a total of 705 events on AMR101 and 901 events on placebo. We see that nonfatal MI made the largest contribution to the number of events to the primary endpoint, with 205 events on AMR101 and 280 events on placebo.

AMR101 was also superior to placebo in time to each individual component of the primary endpoint, with nominal statistical significance. We see that nonfatal MI and coronary revascularization have p-values of less than 0.0001.

Here describes the characterization of

follow-up for the primary endpoint. Sixty-nine percent of patients were censored at the end of study without experiencing a 5-point MACE event, 1.4 percent of patients were censored for non-CV death, and 10 percent of patients were censored before the end of the study. This last category are the patients who were lost to follow-up.

I'll now discuss sensitivity analyses for the primary endpoint. We addressed the impact of patients who were lost to follow-up using data from retrieved dropouts. Retrieved dropouts were defined as subjects who discontinued treatment and who did not experience a 5-point MACE event prior to treatment discontinuation and remained in the study until occurrence of either a 5-point MACE event or the end of the study.

In other words, we are having the missing follow-up of patients that did not have a known event represented by the follow-up after treatment discontinuation of those patients on the same treatment arm who discontinued protocol treatment.

The retrieved dropout set comprised of 1,455

subjects, 665 of whom were on AMR101 and 790 on placebo. Of these 1,455 subjects, 1,170 were followed until the end of the study and 285 experienced an event, 126 of whom were on AMR101 and 159 on placebo. For the analysis, remaining time to an event was imputed using a piece-wise exponential model.

Displayed here are the results of the multiple imputation retrieved dropout analysis. The hazard ratio is 0.776 and the upper bound and the 95 percent confidence interval is 0.852. We see that the results are similar to the protocol specified analysis. A tipping-point analysis was performed by the sponsor. Event rates amongst subjects with missing follow-up were chosen based on 4 reference groups.

The first reference group is based on data from the overall placebo arm. The second reference group is based on pooled placebo and AMR101 patients who are off drug in study, or ODIS, at any time during the study. The third reference group is based on first-year post-randomization data for

pooled placebo and AMR101 patients who were ODIS at any time during the study, and the fourth reference group is based on data from pooled placebo and AMR101 patients within the first year of the study.

Here are the results of the tipping-point analysis. The column on the far left are the event rates per 1000 patient-years that were imputed on placebo patients with missing follow-up. The row on the top is the event rate imputed on AMR101 patients with missing follow-up relative to placebo. Overall hazard ratios, confidence intervals, and p-values are reported.

The results in the red boxed area are not significant. We see that, depending on the reference group, the event rate amongst subjects who were lost to follow-up in the AMR101 group needs to be between 3.7 to 4.3 times greater than the event rate of those in the placebo group in order to tip to a non-significant result. We also see that the largest point estimate, or the hazard ratio, that still corresponds to a significant result is 0.91.

Based on the results of the tipping-point analysis and coupled with the retrieved dropout analysis, we conclude that efficacy findings on the primary endpoint are robust when addressing missing follow-up.

I'll now discuss results on subgroup analyses. This slide displays the results for subgroup analyses for risk category sex, age, and race. We see that there's a nominally significant quantitative interaction in the age subgroup. The effect of AMR101 seems less in the elder group. All the subgroup analyses results were numerically in favor of AMR101. No qualitative subgroup by treatment interactions were identified. In other words, there is no evidence that treatment effects within levels of a subgroup category are in the opposite direction.

I'll now discuss results for secondary endpoints. AMR101 was superior to placebo in time to 3-point MACE. The hazard ratio is 0.735 and the upper bound of the 95 percent confidence interval is 0.83. As with 5-point MACE, nonfatal MI made

the largest contribution in terms of the number of events. Here are the results of the remaining secondary endpoints in the testing structure in order. We see that all but the last endpoint of mortality is statistically significant.

Next, the clinical pharmacology reviewer, Dr. Yunzhao Ren, will present his assessments.

FDA Presentation - Yunzhao Ren

DR. REN: Thank you, Dr. Crackel.

Good morning, everyone. My name is Yunzhao Ren, the clinical pharmacology reviewer for this efficacy supplement of AMR101 . I will now present the clinical pharmacology related topics of this submission.

I'll first introduce the PK characteristics of AMR101 and its active metabolite EPA, followed by results of pharmacodynamic, or PD biomarker, from the REDUCE-IT trial, especially the results of triglyceride and LDL-C. At the end, I will spend some time discussing the potential interference with statin absorption by mineral oil in the REDUCE-IT trial because mineral oil was used as

matching placebo in this study.

Following oral administration, AMR101 is de-esterified in the small intestine to EPA, which is absorbed into human body and metabolized through beta oxidation pathway as other dietary fatty acids. The half-life of circulating EPA in human body is 89 hours. Conversion of EPA to docosahexaenoic acid, or DHA, in Omega-3 unsaturated fatty acid with longer chain is negligible in human body.

Following 12 weeks of 2-gram BID treatment in MARINE trial, EPA plasma concentration increased 4.4-fold in AMR101 group and remained at about the baseline level in placebo group. However, EPA serum concentrations measured from REDUCE-IT trial were considered unreliable, as the storage duration of PK samples was not covered by the stability obtained from a validated bioanalytical assay.

This table summarizes the medium values of major PD biomarkers at baseline and at year 1 or year 2 post-baseline in the REDUCE-IT trial. Of note, hs-CRP was only scheduled to be measured at

one post-baseline time point in REDUCE-IT trial, which was at year 2. Most of the other lipid biomarkers were scheduled to be measured annually.

As you may notice from the table, the baselines of these PD biomarkers are similar between two treatment groups, however, all these PD biomarkers, except LDL-C derived values, demonstrate an opposite trend of change from baseline between two treatment groups at year 1 or year 2. This opposite trend of change from baseline was also observed for non-HDL-C, ApoB, and remnant lipoprotein cholesterol post-baseline values, which are not shown here.

If we arbitrarily use 10 percent change from baseline as a cutoff, there was a reduction of a triglyceride by 18 percent and reduction of hs-CRP by 14 percent from baseline in the AMR101 group. On the other hand, there was an increase of LDL-C by 10 percent and an increase of hs-CRP by 32 percent from baseline in the placebo group. Because different methods were used to measure or to calculate LDL-C values in the REDUCE-IT trial,

it is worth a table to distinguish them. The measurement of LDL-C by standard ultracentrifugation method was only available at baseline and at year 1.

More than 90 percent of LDL-C derived values at baseline and more than 96 percent of LDL-C derived values at year 1 were results from the ultracentrifugation method. If the ultracentrifugation results were not available by priority, the LDL-C value would be derived from the direct measurement by affinity purification, followed by Friedewald calculation method and the Hopkins calculation method.

The table demonstrated that regardless of which method was used, the LDL-C medium value increased about 10 to 13 percent from baseline in the placebo group. The LDL-C between-group differences were majorly contributed by increase from baseline in the placebo group. The differences ranged from as small as 7 percent, or 5 milligram per deciliter, by ultracentrifugation method, to 12 percent or 10 milligram per deciliter

by the Hopkins method.

Reduction of triglycerides is the approved indication of Vascepa. Here we present the time profile of triglyceride change from baseline in the REDUCE-IT trial. For the placebo group, there was about a 2 percent slight increase of median value from baseline, starting at day 120, which was the earliest post-baseline time point available, followed by stabilization until the end of year 2. After that, the profile demonstrated a slightly decrease in trend. For the AMR101 group, there was about 20 percent reduction of medium value from baseline, starting at day 120 followed by slightly decreasing trend afterwards.

The LDL-C time profile by the Hopkins method is depicted here. Of note, the LDL-C time profile by the ultracentrifugation method is not available because it was only scheduled to be measured at the year 1 post-baseline time point. There's only one time point.

For the placebo group, the LDL-C Hopkins medium value increased about 10 percent, starting

at day 120 and stabilized until the end of year 4. For the AMR101 group, the LDL-C median Hopkins value decreased about 1 percent from baseline, starting at day 120 and stabilized until the end of year 4. A similar trend of the increase of LDL-C from baseline in the placebo group was observed if the Friedewald method is used.

For the rest of my presentation, I will discuss the potential interference of mineral oil with statin absorption. I will start with the assessment of the potential clinical pharmacology mechanism of this drug interaction followed by some indirect evidences supporting this hypothesis. At the end, I'll demonstrate the results from some exploratory analysis, evaluating the effect of LDL-C on the primary endpoint.

Mineral oil, or liquid paraffin, is a light mixture of long-chain alkanes from a mineral source, which can hardly be absorbed in the human GI tract, and therefore is used as an over-the-counter lubricant laxative. The recommended dose for mineral oil for constipation

in is 15 to 45 mL per day. The dose of mineral oil used in placebo in the REDUCE-IT trial is 2.5 mL BID.

Due to its chemical property, mineral oil can be a good solvent for lipophilic compounds and conceivably can function as a vector to reduce the absorption and to facilitate the excretion of mineral oil dissolved lipophilic compounds from the human GI tract.

Although there was no dedicated drug interaction study conducted to evaluate the effect of mineral oil on statin absorption, the effect of mineral oil on lipophilic vitamin absorption was well documented in the last century. The reasons we selected this beta carotene paper authored by Dr. Steigmann is because, first, it was relatively a long-term study; second, it was a crossover study; and third, food was provided as the only source of beta carotene for the subjects and the diet in this study was strictly controlled for the beta carotene content.

The table summarizes the beta carotene mean

plasma concentration in subjects following a 4-week administration with different doses of mineral oil under different conditions.

First, mineral oil minimally interfered with absorption of diet sourced to beta carotene if the mineral oil was taken separately from the meal. However, mineral oil interfered with diet sourced to beta carotene absorption when taken with lunch every day. The interference is more prominent if the same daily dose of mineral oil was taken with every meal when compared with just one meal.

When mineral oil was taken with every meal, there's a clear dose-dependent reduction of beta carotene absorption. It is surprising to note that mineral oil volume as small as 2.5 mL per meal could reduce beta carotene plasma concentration by 16 percent. By considering the food volume, it's probably 100 times of the mineral oil volume in this study. Of note, the dose of mineral oil used in the REDUCE-IT trial is 2.5 mL BID.

Chemically, statins are less lipophilic than beta carotene. The second column of this table

list the LogP value of statins used in the REDUCE-IT trial. The greater the LogP value, the more lipophilic of the compound. For reference, the LogP value of beta carotene is 17.6, which is higher than any statins listed in this table. Therefore, based on the results from the beta carotene study, it is expected that the interference with statin absorption by mineral oil is unlikely if they are administered separately.

In the REDUCE-IT trial, patients were instructed to take AMR101 or mineral oil 2 grams, or 2.5 mL, in the morning and in the evening with meal every day. Meanwhile, according to the approved statin dosing regimens listed in the third column in this table, statins should be taken once daily with or without food. Therefore, there's a potential of co-administration of mineral oil and statin at the same time in the REDUCE-IT trial.

Because there's a lack of dedicated drug interaction study for mineral oil and statins, we can only seek for indirect evidences. The cleanest comparison from the clinical pharmacology

perspective is to compare studies in the same context of drug treatment, and the best control comes from the completed clinical studies from AMR101 program.

Amarin has conducted three phase 3 studies for AMR101: MARINE trial in patients with severe hypertriglyceridemia; ANCHOR trial in patients with persistent triglyceridemia and high risk for cardiovascular disease; and the REDUCE-IT trial in patients with cardiovascular disease or at high risk for cardiovascular disease.

The BID dosing regimen of 2 grams of AMR101 or 2.5 mL mineral oil was the same across all three studies. Other than the differences in patient population, the major difference between these three studies is background statin treatment. In the MARINE trial, only a quarter of patients were on statin treatment, whereas all patients in the ANCHOR trial and the REDUCE-IT trial were on statin treatment.

Coincidentally, the LDL-C value, as all measured by ultracentrifugation here, increased

from baseline in mineral oil group with similar extent in the ANCHOR trial and REDUCE-IT trial, but reduced from baseline in the MARINE trial. This suggests that the remarkable LDL-C increase from baseline in the mineral oil group in the REDUCE-IT may be statin dependent, which is an indicator of potential interference of mineral oil with statin treatment.

The second indirect evidence came from the pattern of LDL-C increase from baseline in mineral oil group from the REDUCE-IT trial. We noticed that patients in the mineral oil group on background low-intensity statin treatment had a greater LDL-C increase from baseline than patients on moderate-intensity statin, followed by patients on high intensity statin treatment.

The trend is the same for both absolute values and the percentage values. Consistently, there were also more proportions of patients of the mineral oil group on low-intensity statin treatment that experienced LDL-C increase from baseline than patients on moderate- or higher intensity statin

treatment. However, all these trends were not observed in the AMR101 group.

This pattern can be explained by the established dose-response relationship between statin and its LDL-C reduction effect. As shown in this figure, by plotting available data from approved drug labels, all 4 major statins used in the REDUCE-IT trial demonstrate a typical Emax dose-response relationship on LDL-C reduction from baseline. The lower the statin dose, the steeper the LDL-C reduction rate.

It is known that all these 4 statins follow reasonably linear PK within the therapeutic range. Therefore, if there's an interference with statin absorption, the interference is expected to have a linear effect on PK, and the linear PK interference with statin will demonstrate a nonlinear effect on LDL-C reduction, based on this Emax dose-response relationship.

This will be translating to a pattern that at the low-intensity end, the PK interference will result in a steeper impairment on LDL-C reduction

compared to the impairment at the high intensity end. And pardon me showing the observed pattern one more time. The trend of steeper LDL-C increase from baseline in the low-intensity statin group was observed in the mineral oil group, but not in the AMR101 group.

Here are some inferences from our assessment. First, the interference with statin absorption by mineral oil is unlikely if they are administered separately. However, this interference cannot be excluded if mineral oil and a statin are co-administered because of the relative comparable volume of mineral oil and the statin tablet. The dissolution of certain amounts of statin into the mineral oil cannot be neglected when they are mixed together in a human GI tract.

Although this dissolution of statin in the mineral oil may be diluted by a relative large volume of food, if two drugs were taken together with the meal, the food alone reduces the absorption of most of the statins according to all the drug labels of the statins.

Two indirect evidences support the potential interferences with statin absorption by mineral oil. First, the LDL-C increase in the mineral oil group is accompanied by concomitant statin background treatment. Second, the pattern of LDL-C increase from baseline in the mineral oil group is consistent with the established dose-response relationship between statin and LDL-C reduction.

Regardless of the mechanism of LDL-C increase from baseline in the mineral oil group, the clinical meaning of about 10 percent increase of LDL-C from baseline in the placebo group needs to be interpreted, as higher LDL-C level is known associated with the increase of risk of cardiovascular outcome and the imbalanced LDL-C value between the placebo group and the AMR101 group may bias the study results.

From a clinical pharmacology perspective, this question can be answered in a way similar to an exploratory biomarker analysis in which we evaluated the adjusted AMR101 treatment effect size by introducing LDL-C absolute values and change

from baseline values as continuous covariates in the Cox proportional hazard model for the primary endpoint.

Here, the analysis were conducted in the same predefined context of the primary analysis with the same stratification factors. In this analysis, LDL-C day 120 post-baseline value by the Hopkins method was chosen because this combination has the largest post-baseline sample size, and the median LDL-C value appear stabilized on day 120. In addition, the Hopkins method has the greatest between-group differences of post-baseline LDL-C values, representing the worst-scenario case.

As displayed in this table, neither the absolute LDL-C values nor the change from baseline values reveal a significant change on the effect size of AMR101 treatment on the primary endpoint. The hazard ratios of LDL-C covariates per unit value on the primary endpoint are numerically close to 1 with a generally flat slope, and the ballpark effect of these flat slopes could be roughly estimated, as shown in this slide.

On day 120, median LDL-C increased 7.3 milligrams per deciliter from baseline in the placebo group and decreased 1.6 milligram per deciliter from baseline in the AMR101 group. This about a 9-milligram per deciliter LDL-C between-group difference can be roughly translated into an increased risk by 3 percent in the placebo group.

To the same extent, a 3 percent increase of risk in the placebo group was obtained if we use the LDL-C percentage change from baseline value on day 120. In the background material of the AC meeting, we estimate a 3.1 percent increase of risk in the placebo group by using the year 1 value.

Of note, all of these analyses are exploratory by nature. Because the post-baseline LDL-C covariates were used in the model, all the limitations of post-baseline analyses will apply here. For example, even if LDL-C values from day 120, the earliest post-baseline time point, was selected, scores of MACE events had already occurred and hundreds of patients did not have

their lipid profile examined on day 120. The sample size on day 120 was about 440 subjects or about 5 percent smaller than the sample size at randomization.

This slide concludes my presentation, and I'll introduce Dr. Crackel back to the podium for more statistical remarks.

FDA Presentation - Roberto Crackel

DR. CRACKEL: I'll now present an additional statistical analysis and give conclusions. From a statistical perspective, we can do an indirect comparison with an inert or true placebo using the study data if we knew how much risk increase mineral oil causes in comparison to inert placebo.

From the study results, the upper bound of the hazard ratio is less than or equal to 0.83. If we assume the hazard ratio of mineral oil, compared to an inert placebo, is equal to k, then the hazard ratio of AMR101, compared to inert placebo, is less than or equal to 0.83 times k. Therefore, as long as we have k is less than 1.20, we have that the hazard ratio of AMR101, compared to inert placebo,

is less than or equal to 1.

Therefore, as long as mineral oil does not increase the risk over inert placebo by 20 percent, the study has demonstrated superiority of AMR101 over inert placebo. However, the hazard ratio between mineral oil and inert or true placebo is unknown.

As discussed by an exploratory analysis conducted under the clinical pharmacology section, a 9-milligram per deciliter LDL-C between-group difference in the REDUCE-IT trial can be roughly translated into an increase of cardiovascular risk by 3 percent in the placebo group.

Here, we revisit this topic by appealing to literature results. A paper published in the Lancet in 2010 summarized a meta-analysis of randomized clinical trials, comparing statin treatments, including trials using different intensity of statins, in evaluating CV risk reduction. One of these trials included in the paper, the TNT trial, had a similar LDL-C baseline mean value compared to the REDUCE-IT trial, which

was also less than 100 milligrams per deciliter.

The effect of increase of CV risk in patients on lower intensity statin treatment compared to patients on higher intensity statin treatment was translated into a percentage increase of the relative risk per milligrams/per deciliter, by the difference of LDL-C levels between low- and high- intensity statins as summarized in the last column.

As shown in the table, the rate of percentage increase of the hazard rate ranged from as small as 0.44 percentage per milligrams per deciliter LDL-C in the SEARCH trial to 1.17 percentage per milligrams/per deciliter, LDL-C in the TNT trial. Based on the meta-analysis, the percentage increase of relative risk is 0.91 percentage per milligrams/per deciliter increase of LDL-C.

In the REDUCE-IT trial, there was an observed 9 milligrams per deciliter LDL-C difference between treatment arms at day 120 from baseline. Based on the rate estimated from the

meta-analysis, this translates into an 8.2 percent increased risk versus inert placebo. We therefore conclude that the observed LDL-C increase in placebo patients is unlikely to render the study conclusion on the primary endpoint invalid since a 20 percent increase is needed to tip the study conclusion.

In conclusion, the study has demonstrated superiority of AMR101 over mineral oil placebo in 5-point MACE. Results of analyses addressing the impact of patients with missing follow-up are robust. Further, the effect of LDL-C increase in placebo patients on CV outcomes appears to be of small magnitude and unlikely to invalidate conclusions.

I now welcome back Dr. Chowdhury to discuss clinical safety overview.

FDA Presentation - Iffat Nasrin Chowdhury

DR. CHOWDHURY: Thank you, Dr. Crackel.

I will begin the safety review with a discussion about study drug exposure. Exposure was slightly higher in the AMR101 treatment arm, 4.4

years in 4,083 patients as compared to 4.1 years in 4,077 patients on placebo. These findings are consistent with the lower rates of study discontinuation, treatment discontinuation, and deaths observed in the AMR101 arm.

Regarding adverse events leading to study drug discontinuation, overall, 656 patients discontinued study drug due to an adverse event, approximately 7.9 percent in AMR101 compared to 8.2 percent on placebo; most discontinuations due to adverse events or due to gastrointestinal disorders, diarrhea, and nausea.

Rates of adjudicated non-cardiovascular deaths were similar between the two treatment arms and expected for the population. The most frequent causes of non-cardiovascular death were in the neoplasms system organ class followed by infections. Within the neoplasms category, lung, pancreatic, and colorectal malignancies were most frequently reported. Within the infections category, pneumonia and sepsis were most frequent.

Serious adverse events were also consistent

with expected events in the patient population. One-third of the patients in the overall trial reported at least one serious adverse event, and the incidence rate of SAEs was similar in the two treatment arms. The most frequent events were reported in the infection system organ class followed by neoplasms. Within infections, pneumonia and sepsis were most frequently reported SAEs, and within neoplasms, prostate and colorectal malignancies were most common SAEs.

In REDUCE-IT, the most common adverse events occurred in the categories of infections and infestations, musculoskeletal and connective tissue disorders, and gastrointestinal disorders. Preferred terms, which occurred greater than equal to 3 percent in AMR101, the difference was greater than or equal to 1 percent from placebo, were AE terms such as musculoskeletal pain, peripheral edema, and gout.

A literature search for peripheral edema and gout and Omega-3 fatty acids did not show any association with these adverse events, therefore,

1 the clinical significance of these small imbalances
2 is unclear.
3 We examined blood pressure changes during
4 the trial. Differences in mean systolic and
5 diastolic blood pressure between arms were not
6 clinically meaningful. The between-arm difference
7 in systolic blood pressure was 1.5 millimeters
8 mercury greater in placebo at year 1, but the
9 magnitude of the difference was smaller at
10 subsequent study visits, including the final study
11 visit when the difference was only 0.6 millimeters
12 mercury.
13 Similarly, diastolic blood pressure was 0.6
14 millimeters mercury greater in the placebo arm at
15 year 1, but the difference was only 0.3 millimeter
16 mercury at the final visit with decreases from
17 baseline in both arms. Furthermore, analysis of
18 potentially clinically significant changes in blood
19 pressure, for example, the proportion of patients
20 with increases in systolic blood pressure greater
21 than or equal to 160 millimeters mercury, did not
22 show any consistent trends favoring either

treatment arm.

Regarding bleeding-related adverse events, a higher proportion of patients in the AMR101 arm experienced bleeding-related adverse events. Note that this slide does not include hemorrhagic strokes, which were an adjudicated component of the primary efficacy endpoint. Because there were very few hemorrhagic strokes overall in the trial, 13 in AMR101 and 10 on placebo, excluding these events had negligible effect on the safety analysis.

From the AE data set, there was an approximately 2 percent higher incidence of patients experiencing any bleeding event in AMR101 compared to placebo, 11.8 percent versus 9.9 percent. Serious bleeding occurred in 2.7 percent of patients in the AMR101 group versus 2.1 on placebo; 3.1 percent of patients on AMR101 and 2.8 percent of patients on placebo had GI bleeding.

The majority of events occurred in a category of other bleeding. The most frequent terms under this category were contusion,

hematuria, and epistaxis. Although not shown on this slide, bleeding events associated with a fatal outcome occurred in 0.5 percent of patients on AMR101 and 0.6 percent of patients on placebo.

This slide shows bleeding events, excluding hemorrhagic stroke, by baseline antithrombotic use. In the subset of patients not taking antithrombotics at baseline, the number of bleeding events was small in both treatment arms, and we cannot exclude the possibility that there was no meaningful difference in the number of patients experiencing events between arms.

Consistent with the overall population, the rate of bleeding was greater in the subset of patients taking antithrombotic medications who were also on AMR101 versus patients taking antithrombotic medications who were on placebo; 12.5 percent versus 10.4 percent.

Moving on to the topic of cardiac arrhythmia, this slide shows the CEC definition, which is arrhythmia that resulted in hospitalization during or within 24 hours of the

termination of the last episode for treatment or required continued treatment. Although the CEC adjudicated atrial, ventricular, and bradyarrhythmias, only atrial fibrillation and atrial flutter findings were of interest.

There was an increased risk of events of atrial fibrillation or atrial flutter requiring hospitalization among patients in AMR101 compared to placebo. Positively adjudicated Afib/flutter was reported at 3.1 percent in AMR101 and 2.1 percent on placebo.

This slide shows time to first onset of atrial fibrillation and flutter requiring hospitalization of greater than or equal to 24 hours. The curve diverges at around 250 days, with patients on AMR101 showing increased risk as compared to placebo.

This is a stratified analysis of Afib/flutter requiring hospitalization by a Afib/flutter history at baseline. The incidence of atrial fibrillation/flutter was higher in a subset of patients with self-reported previous history.

The higher estimate of the hazard ratio suggests that the risk may be greater in patients with a history of atrial fibrillation/flutter, but the results are not conclusive.

In conclusion for safety, there was an increased risk of adjudicated atrial fibrillation or flutter in AMR101 compared to placebo, 3.1 percent versus 2.1 percent. There was an increased incidence of bleeding events with AMR101 compared to placebo. Otherwise, the safety profile was generally consistent with prior labeling for Vascepa.

The overall conclusions are, for efficacy, REDUCE-IT demonstrated statistically significant and clinically meaningful reduction of the risk of major adverse cardiovascular events among patients treated with AMR101 compared to placebo in the trial population. Efficacy results were robust to a number of sensitivity analyses. Use of mineral oil placebo is unlikely to invalidate the study conclusion for the primary outcome. The applicant's proposed indication is broader than the

trial population.

For safety, the trial identified two new safety issues, atrial fibrillation and bleeding. Despite these findings, the benefit-risk profile remains favorable. This is the end of the FDA's presentation for this application.

Clarifying Questions to FDA

DR. BURMAN: Thank you very much.

We will now go to clarifying questions for the FDA. Please remember to state your name for the record before you speak, and if possible, please direct your question to a specific presenter. Please, Dr. Ellenberg?

DR. ELLENBERG: I would like to have a better explanation of the sensitivity analysis for missing data in the primary analysis. You talked about a retrieved dropout. That's not something I'm particularly familiar with. It sounds to me like it just means that those people were continued to be followed and you included them, but I don't know how you imputed the values for people who were lost to follow-up who hadn't had an event.

Could you give us some more explanation of that?

DR. CRACKEL: Sure. Patients who were lost to follow-up were represented by patients who -- excuse me. Patients who were lost to follow-up who did not have a known event were represented by patients who discontinued protocol treatment, yet remained in the study. So the imputation starts at the time that the patient was lost to follow-up.

I'm not explaining this clearly. Patients who were lost to follow-up -- Wow. Sorry.

DR. BURMAN: It would be fine if you want to think about it for a minute, and we can come back to you.

DR. CRACKEL: Yes, please.

DR. BURMAN: Of course.

DR. ELLENBERG: I'm used to more things like under a missing at random assumption, where patient characteristics and characteristics of people who didn't drop out were considered in making the imputation. So I'm just wondering how this

compares with that.

DR. LI: My name is Feng Li. I'm the statistical team leader for this submission. Basically, the primary analysis assumed event time for subjects who were lost to follow-up were censored. So it assumed the non-informative censoring or missing at random. In this sensitivity analysis, we assumed that the event rate of those who were lost to follow-up are similar to subjects who are retrieved dropouts, and means that they discontinued treatment but remained in study without event before discontinuation. So this is based on a different assumption.

DR. BURMAN: Does the FDA have a comment?

DR. SHARRETTS: I think what your question was is the type of analysis, and you mentioned a missing-at-random analysis. But a missing-at-random analysis is not the appropriate type of analysis to do to impute data because it assumes that people who are getting the drug behave the same way as people who are not getting the drug.

So this type of analysis is a missing, not at random, and they impute the data for missing patients based on patients who are in the same arm. So the placebo patients are compared against placebo and the treatment patients are compared against treatment. They used patients who discontinued drug but stayed in the study to represent patients who quit the trial and who also would have been patients who discontinued the drug.

DR. ELLENBERG: I still don't really understand what data were used to make the -- was it a single imputation? You did a multiple imputation? And if you did, based on what data? This may be a small point; I just didn't --

DR. CRACKEL: The imputation was based on data from --

DR. BURMAN: Dr. Crackel, please state your name.

DR. CRACKEL: Sorry. Roberto Crackel. The imputation was based on data from retrieved dropouts. So those patients who discontinued treatment but did not experience an event or MACE

event prior to treatment discontinuation remained in the study until either a further event, or an event, or the end of the study.

DR. ELLENBERG: Yes, I understand that, but is what you did is then take sort of the average of those patients, and then impute that as a single imputation for the people who were lost to follow-up?

DR. WANG: This is Yun Wang, acting deputy director for the Division of Biometrics II. I would like to address Dr. Susan Ellenberg's question about retrieved dropout analysis we did.

We had patients discontinue the treatment. Some of those patients were followed up in the study. Some of them lost follow-up. So for those patients who were followed up, we have the time-to-event data. So we used that data. We supposed those patients who discontinued treatment behaved similar, no matter whether they were still in the study or they're not in the study anymore.

So we used observed data from the patients who still were in the study. We estimated the

hazard rate from those patients, then we randomly drew a hazard rate from that estimate, then used that random draw, and we imputed 100 times, say, for those patients what's a possible time to event for those patients lost to follow-up. Basically, it's not a single imputation; it's a multiple imputation.

DR. BURMAN: Thank you. If we have any further questions on that from you or from the panel, they can discuss them later.

Dr. Wilson?

DR. WILSON: Peter Wilson. In your preliminary data, there were some extra analyses, according to bleeding risk post hoc, your Appendix L, and you didn't show those. The sponsor showed those, and I'm especially interested in aggregations of persons on one or more antiplatelet therapies.

Do you have any data on that?

DR. SHARRETTS: I do have that data, and I think I have it in my backup slides from the intro. I brought that back.

DR. WILSON: So both for baseline and for during trial, on trial.

DR. SHARRETTS: Yes. I think I only have like three backup slides, so it's one of them.

DR. WILSON: But that would be something I think we would all be very interested in seeing, your analyses as well, also, and later from the sponsor, for further discussion on that.

DR. SHARRETTS: The reason we included them in the background packages is to try to do an exploratory analysis to see if there was any evidence of a specific drug interaction with either AMR101 or with placebo, with any particular antithrombotic agent. Now, the three most commonly used antithrombotic agents were aspirin, clopidogrel, and warfarin. All other agents, the numbers were very small.

So when we carved them out, we tried to see what the events rates were like; and, generally, what we saw is the same imbalance. There was about a 20 percent increase in bleeding in patients on AMR101, regardless of what their background therapy

was. So to carve out the data even more, we tried to select patients who were taking aspirin only and no other antithrombotic -- clopidogrel only and no other antithrombotic, and warfarin only and no antithrombotic.

Now granted, these numbers start to get very small, and it's challenging to determine what type of analysis to do, because if you do a baseline analysis, the patient may not actually be on that drug when you do it. But if you do a post-baseline analysis, you're introducing a post-randomization variable to analyze it.

So there are limitations to these, but, generally, what we found was that the trends were similar. There was a slight increase in bleeding with AMR101 compared to placebo, regardless of what the background was.

Were you able to find my -- it's at the end of my presentation. I think I have three backups. Are they all compiled together? It was the introductory remarks.

STAFF MEMBER: Which backup?

DR. SHARRETTS: I'm not sure. I only have three backups, and I saved that one because I thought we might get a question on it.

DR. WILSON: As a follow-up, though, especially the sponsor's slide number 80, have you performed an analysis similar to theirs, with aggregation of one or more antiplatelet therapies, on baseline or during trial?

DR. SHARRETTS: I think we did do analyses by 2 antithrombotics and 3 antithrombotics. We didn't include those in our background package because we didn't think they were additionally informative. I went the other way. I went to the patients that had only one antithrombotic because I thought that was more informative.

One of the analyses that we did that's in the backgrounder was to compare patients who were on low-dose aspirin, which was defined as aspirin doses less than 100 milligrams per day versus higher doses of aspirin.

DR. FAJICULAY: Do you have the number [off mic]?

(Pause.)

DR. SHARRETTS: So the analysis we did was by the single -- the ones that we showed were by the single agent because the overall category includes people who are on more than one agent. So it might be if a patient's on aspirin, they might also be on clopidogrel. They might also be on ticlopidine. They might also be on warfarin.

So those already account for people beyond multiple agents, and if you try to tease it down to 2 specific agents, the numbers just get very small, and they're hard to interpret.

DR. KONSTAM: This is Marv Konstam. I just would love to see warfarin.

DR. SHARRETTS: Here's warfarin only. So there's an increased risk of bleeding on warfarin only plus AMR101.

DR. KONSTAM: I didn't mean warfarin only; I meant all patients on warfarin.

DR. SHARRETTS: I don't think I have that in my backup slide set. I think the applicant showed the bleeding for the overall group.

DR. BURMAN: Do you have anything further on this slide, Dr. Sharretts?

DR. SHARRETTS: In your presentation on safety, we have the overall aspirin, clopidogrel, and warfarin; right?

(Pause.)

DR. BURMAN: We can maybe bring this back up.

DR. SHARRETTS: No. We only showed it by all.

DR. BURMAN: Dr. Sharretts, do you have any further comments at the moment? We can bring it up and maybe ask the sponsor later as well.

DR. SHARRETTS: Alright.

DR. BURMAN: Thank you. Dr. Newman?

DR. NEWMAN: Connie Newman. My question is about the increase in CRP in this trial, and I believe it was increased in ANCHOR, one of the phase 3 trials that was shorter. How do you interpret this?

DR. REN: This is Yunzhao Ren, clinical pharmacology reviewer. Can you go to my slide, the

clinical pharmacology slide, number 33. So here, as I mentioned, hs-CRP post-baseline was only measured at one time point, which is at year 2. As you can see, the sample size is smaller than all the other time points. We introduced these hs-CRP absolute values and changed from baseline values, and did the same exploratory analysis to see its effect on the primary endpoint.

You can read the last two lines. At year 2, post-baseline time point, there is 0.65 milligram per liter difference between the two treatment groups, which the placebo increased and the AMR101 group decreased. That can be roughly translating to very limited, about 0.3 percent of increase of risk in placebo group. Here, if you use another category, which is not the absolute value but the percentage change, it's 0.1; it's even less.

To be more consistent, I have another slide, my slide 35. Here, compare both the absolute value and change from baseline value in all three studies conducted by Amarin. As you can see in terms of the change from baseline value, it's quite

consistent in placebo group across all three studies, and also the same thing happened in AMR101.

DR. BURMAN: Thank you.

DR. NEWMAN: Thank you.

DR. BURMAN: Dr. Posner, on the phone?

DR. KONSTAM: May I follow up to that?

DR. BURMAN: Hold on.

DR. POSNER: Yes, I am on the phone. Sorry about that. I had to unmute.

DR. BURMAN: Sure, Dr. Posner; please go on.

DR. POSNER: Yes. I had two questions, one which may have been answered. That was, in the anticoagulant study, was there a subgroup that looked at the NOACs versus warfarin and aspirin?

DR. SHARRETTS: This is John Sharretts. We did look at NOACs, but again, because the number of patients on any NOAC was very small, those analyses were not interpretable. Looking at my -- it was in the low hundreds of patients in the entire trial who were on any NOAC.

DR. BURMAN: Thank you.

DR. POSNER: Well, I can understand that because they are sort of new. I had another statistical question. They have a non-Caucasian subgroup listed, and it's very small. And I know a lot of the study was the Japanese study, but are the numbers for African Americans and Native Americans included in that group, and can they be broken out? And I think particularly African Americans, who are hypertensive, high lipid, and in the high type 2 diabetic groups, whether they were studied.

DR. YANOFF: Perhaps the applicant could show us further breakdown of the demographics, if you have it.

DR. JULIANO: Actually, while the team is looking for further breakdown -- oh, here we have it. Slide 4 up, please.

This is baseline characteristics by sex, race, and ethnicity. You can see here about 90 percent of the patients were white; about 2 percent, African American; a little over 5 percent, Asian; a little less than half a percent, American

Indian or Alaskan Native; and less than 0.1 percent Hawaiian or Other Pacific.

DR. POSNER: Thank you.

DR. JULIANO: I would like to point out -- could I see, just while I'm here, real quick, the primary endpoint by white versus non-white, the callout of that Kaplan-Meier? Just because I'm not sure if this was one that Dr. Bhatt presented. That should be in our backup slides, if the team could get that quickly.

Essentially, you don't see a large differential between the groups -- there we go; slide 2 up, please. You don't see a large differential in benefit between the two treatment groups, an interaction p-value that does not suggest a difference in benefit. And if anything, the hazard ratio shows a potentially larger relative risk reduction; although, again, not statistically different between the groups, but certainly not a suggestion of less benefit within the non-white group.

DR. BURMAN: Thank you. We have about

15 minutes before the break. Dr. Konstam, you had a very quick follow-up.

DR. KONSTAM: Well, yes. It was a follow-up to the question about CRP. We're looking at each of these things in isolation, and what I'm struggling with is there are a few different things going on, and we don't know to what extent. For example, an increase in LDL cholesterol and an increase in CRP are overlapping, and then representing an increase in cardiovascular risk or they're on top of each other.

The other thing is there is a slight increase in blood pressure, about a millimeter of mercury, I think; something like that, depending on when you're looking. It shouldn't be much. I don't know what other biomarkers we're not looking at it, but there's a question of what mineral oil does to absorption; could it affect absorption of antihypertensives? I'm struggling with how you pull that together to be confident that, in aggregate, those things aren't playing a significant role.

DR. REN: This is Yunzhao Ren. I can ask [sic - answer] from a small point of view, and if there are anymore comments from our colleagues, I will defer to them.

As you can see, there are so many biomarkers. If you pick up them one by one, or even you cherry-pick them one by one, it will be endless, like by different time points. You will see some signals there, some signals there, and what is the totality of all these differences you can explain, and whether everything can be contributed by the mineral oil malabsorption effect on all the drugs you administered in this study.

I will say this is an open question. I don't have a specific answer for that. But as you can see, for most of the biomarkers we explored, even includes triglycerides in our background material; all these effects are generally small. If you pick up just one of them, they're not likely to tip the overall conclusion.

If you want to add them all together, then I would question this kind of approach because you

definitely need to pick up those which established clinical meaningful biomarkers. Let's say for triglyceride, even by Amarin's presentation, they are not even convinced that reduction of TG is associated with this tremendous reduction of the cardiovascular event.

DR. KONSTAM: Yes. I take your point --

DR. BURMAN: Marv, hold on one second. Dr. Sharretts wants to mention something.

DR. SHARRETTS: Yes. John Sharretts. Just to add in to Dr. Ren's comments, I think the challenge with looking at something like CRP in addition to LDL, it's very difficult to say if the effects are independent.

If you decrease absorption of statins, and the LDL goes up, presumably this hs-CRP will go up again. I think what Dr. Ren tried to do is with the hs-CRP analysis is that a 0.6 milligram per liter increase in hs-CRP translated to maybe a 0.3 percent increase in hazard ratio. So we thought that's almost insignificant that you can't try to make it additive.

The question with blood pressure, well, that's a little more challenging. What does a 1-millimeter mercury difference portend? I think a 20-millimeter mercury increase in systolic blood pressure doubles the relative risk for cardiovascular events, but we can't even -- I'm not sure if that 1 millimeter is significant; could it potentially have 0.05 over the relative risk ratio? I'm not sure, in terms of the percent on the hazard ratio, that would affect, but again, I think it would be very small.

Then I think with the other issues, we just tried to look at them qualitatively. With the bleeding, I think we tried to pick out did it look like there was any individual antithrombotic with which there was an interaction, and it didn't appear that there was.

We, again, tried to use indirect evidence that we talked about in the backgrounder, that clopidogrel has a very wide exposure-response relationship. So even if you decrease absorption a little, the effect is going to be the same.

Aspirin has an extremely wide dose-response relationship, so whether you take 50 milligrams of aspirin or 1500 milligrams of aspirin, it has the same impact on stroke. That data, we thought there just isn't evidence that those other factors were significantly additive, and that's why we focused on LDL.

DR. KONSTAM: I just would say I take all those points. I still feel a little bit challenged from the conclusion as you've seemed to present it, that you're confident that none of this has an effect. I'm sort of not quite there.

DR. SHARRETTS: John Sharretts again. Well, I would say that that's the reason why we're here. We had our conclusions, but we thought some of these issues are debatable, and that's why we thought it was important to bring it in front of the advisory committee to see what you think.

DR. BURMAN: Thank you. Thank you for that discussion.

Dr. Weber?

DR. WEBER: Thank you. This is Tom Weber.

This is for Dr. Crackel and the analysis you did in terms of the mineral absorption effect on the estimated LDL difference; in effect, understanding it's exploratory but a back-of-the-envelope calculation, and that can be pointed out this is incorrect. But it looked like it would change the absolute risk reduction from 4.8 percent down to 3.0 percent with an NNT of 33, which is clinically meaningful.

But I wanted to just make sure that that can extrapolate. And I can actually ask the sponsors, too, to look at that, if not now, maybe after lunch.

DR. BURMAN: Any comment?

(No response.)

DR. BURMAN: If there are no further comments, we will have time for questions another 10 minutes or so. Thank you.

Let me make a question as well, if I can. Correct me if I'm wrong, but there has not been a direct study specifically looking at mineral oil effect on statin absorption, much less the

1 different kinds of statins, and then measuring LDL
2 after a couple of months, or measuring statin
3 levels in the blood. Those studies have never been
4 done.
5 DR. REN: Yes. This is Yunzhao Ren. Your
6 interpretation is correct. There's no such study
7 that exists.
8 DR. BURMAN: But would be relatively easy to
9 perform. We're not looking for endpoints; we're
10 looking for absorption in pharmacokinetics.
11 Further, my second question is, In the
12 PROVE-IT trial -- and maybe you would know or the
13 sponsor would know -- what time of day were the
14 medications given, and where they actually given at
15 the same time or was there no specification
16 whatsoever that the placebo was given at the same
17 time as the statin?
18 DR. REN: I can answer part of the question
19 from my experience, from the drug labels of
20 statins. If you read all these statin labels, some
21 statins specifically say administer statin at
22 evening or at bedtime because the study was

conducted in such a way -- or even some statin studies show that patients benefit more if the dose was given during night.

I would say most statins just say take once daily, with or without food, anytime. Probably due to the timing of this administration, statins were not well studied.

DR. BURMAN: So if you're correct, the majority of the statins were given in the evening, separated from the placebo or the medication, which was given twice a day.

DR. REN: I want to say the majority, but some of them.

DR. BURMAN: We will ask the sponsor later to comment on that, if they would. Dr. Yanovski?

DR. YANOVSKI: Thanks. Jack Yanovski. This is a question that relates to one of the analyses that the sponsor showed. Did the FDA evaluate the 10-year risk calculations that the sponsor has shown today at all? For instance, when do the confidence intervals not overlap zero for a 10-year risk of an event?

This is sponsor's slide, I guess, 107, and shown several other times. I think it's 107. It's the 10 percent risk versus a much greater risk, suggesting that there might be a subgroup that would more benefit from AMR101. Did the FDA examine that at all?

DR. CRACKEL: No, we did not.

DR. BURMAN: Thank you. Dr. Ellenberg?

DR. SHARRETTS: The FDA did not do these analyses. And actually, that particular analyses I think was the first time that we had seen it. I think my first question, which I think one of the panelist has already raised, is that they showed risk ratios for the primary endpoint versus new onset of Afib. In new onset of Afib, the totals for the less than 10 percent category were very, very small. There was one event in the AMR arm and zero events in the placebo arm.

So I think it would be more informative to see those events on the full population of atrial fibrillation rather than the adjudicated new onset. But I think those are the types of analyses that we

could try to do to create a benefit versus risk profile. I think, overall, in a high-risk cardiovascular population, the effect on MACE is going to far outwe gh the risk of atrial fibrillation, but in a low-risk population, yes, there might be a different calculus.

DR. BURMAN: Thank you. For the record, that was Dr. Sharretts. Dr. Ellenberg?

DR. ELLENBERG: Susan Ellenberg. I have a couple more questions on the analysis. There were about a hundred people who died for non-cardiovascular causes on each arm. Did you account for those using a competing risk analysis? Because once they die for something else, then they're no longer at risk for one of the endpoints in the study. Was that done?

DR. SHARRETTS: I don't think the statistical team did any specific analyses. We did qualitative analysis, which was to look at what the events were. They were very, very similar between arms. I think, as Dr. Chowdhury pointed out, I think lung cancer was the leading cause of death in

both arms.

DR. ELLENBERG: I think it's unlikely that it would make a difference, but, typically, that's what you would want to do, is to account for them because they reduce the denominator as you go on because they're no longer at risk. When you just censor them, the assumption is that they would continue to be at risk, and they are no longer at risk.

So that's one question. The other is there's a sort of curiosity thing. These were highly significant -- oh, sorry?

DR. SHARRETTS: Sorry. John Sharretts again. I think what Dr. Yanoff pointed out to me is there was no difference in the total of non-cardiovascular events so --

DR. ELLENBERG: Yes.

DR. SHARRETTS: -- of non-cardiovascular deaths, so we wouldn't expect to see any difference if we did an analysis accounting for that. If there had been an imbalance, then that might have affected the trial result.

DR. ELLENBERG: I understand that. You just kind of never know what's going to happen when you do that. I agree with you that it's unlikely that there would be an effect. The findings were very, very strong with a very significant p-value, so I was curious about the interim analyses that were done, were 60 percent and 80 percent.

There's certainly not a strong consensus in the clinical trials' community about what the criteria should be for early termination, but I wondered what the boundaries looked like in this study. When you see something with 12 zeros in front of the p-value, where mortality is one of the outcomes, you kind of wonder what the plan was for early termination.

DR. SHARRETTS: This is John Sharretts. I think that question is better addressed to the sponsor because it's about trial design and the statistical methods that they used for the interim analyses.

DR. ELLENBERG: Can I ask one more question, quick question? The 10 percent threshold for the

cardiovascular risk score, was that a prespecified threshold?

DR. SHARRETTS: John Sharretts again. No, that's not prespecified. In fact, the analyses by 10 percent risk are new to today's presentation. That wasn't in the applicant's original background materials.

DR. BURMAN: Thank you. We have five minutes. We're going to take one more question, but we're going to have time at about 2:00 for further questions to the sponsor and the FDA. And maybe the sponsor could be answering two of these three questions that have come up, and if we need to, we can specify them more.

Last question, Dr. Low Wang?

DR. LOW WANG: Thank you. Cecilia Low Wang. I was wondering if the FDA did an analysis of the primary prevention risk category, after you exclude the patients with established cardiovascular disease. What I'm concerned about is that it looks like the benefit of Vascepa was really centered around the patients in the secondary prevention

cohort, and the problem is that the primary prevention cohort included, according to my calculations, about 400 patients who had established cardiovascular disease.

So I'm worried that what we're looking at in that subgroup analysis actually makes the numbers look better than they really are in that primary prevention cohort.

DR. SHARRETTS: Hi. This is John Sharretts. I think I can answer part of that, and some of it I might defer to the applicant. I think, number one, is that the study wasn't powered to show an effect in the CV risk cohort 2, and it only accounted for 30 percent of the patients. I think if we exclude some of the patients, the statistical power is going to get even lower.

Second of all is if you exclude patients, we might end up introducing bias because those patients aren't randomized appropriately. I think we could do those analyses. I don't think we did. But if we thought that was important, we could do them, but it's hard to know how informative they

would be because of those limitations.

DR. BURMAN: Thank you. Last question, Dr. Brittain?

DR. BRITTAIN: I did have one question, but I also just wanted to comment on the last comment, which was it is a baseline characteristic, so there shouldn't be any problem with excluding that. There's no issue with bias. Your other points you make are fine.

The only other question I had, I think other people have asked for this same analysis, but I'm not sure. It's exactly the same analysis, which is combining MACE with the arrhythmias and the bleeding events as if that were the endpoint and doing the time-to-event analysis.

I'm assuming, again, that the treatment group will look very good in that analysis, and, of course, it's sort of an unfair analysis. But if it is still very significant, I think that's an important result. I'm not sure. I've heard other comments that were very similar, and I wasn't sure if it was exactly the same.

DR. SHARRETTS: This is John Sharretts. I think that's something we can take under advisement. I think the challenges with that is, in a post hoc analysis, what events do we include? Do you include all bleeding events, which is about 400 in each arm, many of which are minor -- they're epistaxis and contusions -- or do you limit it to certain types of bleeding events?

Well, I think depending on how you do the analysis, you will get different results. I think with atrial fib and atrial flutter, I think, just on the ballpark, knowing that it was 1 or 200 events in each arm versus 700 and 900 MACE events in each arm, I think the effects are going to be rather small. But again, I think it's something we could consider doing, but there are challenges with doing the analyses post hoc because we know the data, so we can choose what to include in the analysis.

DR. BURMAN: Thank you. Dr. Brittain? No?

For the next minute or so, right before we break -- Dr. Yanoff?

DR. YANOFF: Sorry. I hope I'm not misremembering, but, Dr. Low Wang, I believe the company may have presented the analysis you were looking for in their presentation this morning, and I wonder if they could reshow that for you.

DR. LOW WANG: Actually, I did see that slide, except that they didn't show the hazard ratio. They showed only the adjusted risk difference, the absolute risk difference.

DR. YANOFF: Okay.

DR. BURMAN: Thank you, Dr. Yanoff, as well as Dr. Low Wang. In fact, that's what I wanted to do for the last minute or two, is summarize for the FDA, or the sponsor, specific questions that we'd like them to come back and answer to make it a little clearer.

One that hasn't been brought up, and Dr. Wilson brought it up to me, is -- you want to mention it?

DR. WILSON: For the diabetic patients, we expect to see pretty good care and lowering of A1c closer to target ranges, and we've not seen any

data on that for the diabetic patients; so some discussion, of if someone has an answer that's quick, that would be fine.

DR. SHARRETTS: John Sharretts. I have an answer that's quick. We did analyses of the diabetes data. I believe in both arms, the mean A1c increased by about 0.2 percent from the beginning of the trial to the end of the study. It was almost identical in the two arms.

DR. BURMAN: Thank you. Would the panel mention to the sponsor or the FDA specific questions that you wanted answered? Yes?

DR. NASON: Since someone just around the table -- the cutoff on the 10-year risk score, which is something the FDA hadn't seen before, I thought it would actually -- and since that's not prespecified and something chosen, after looking at the data, I thought it would be interesting if the sponsor could present that on a continuous cutpoint, basically.

You could imagine as a sliding scale on the risk score, you could then look at the effect and

the difference, instead of just fixing it at 10 percent. I think that would be more useful than something that's been chosen ad hoc. So if you could show that, that would be helpful.

DR. BURMAN: Thank you. Please mention your name for the record.

DR. NASON: Martha Mason. Sorry.

DR. BURMAN: Thank you; of course. Other specific issues that came up? Dr. Low Wang?

DR. LOW WANG: Just to mention again, in the sponsor's slide number 92, if you could please tell us the hazard ratio for the primary endpoint in that population, that would be great.

DR. BURMAN: And that will be after the break.

We will now break for lunch. We will reconvene again in the room one hour from now at 1:05. Please take any personal belongings with you. Committee members, please remember, there should be no discussion of the meeting during lunch among yourselves, with the press, or any member of the audience. Thank you.

(Whereupon, at 12:03 p.m., a lunch recess was taken.)

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

(1:05 p.m.)

Open Public Hearing

DR. BURMAN: Good afternoon. We're going to start the OPH 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 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 relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA

1 encourages you at the beginning of your statement
2 to advise the committee if you do not have any such
3 financial relationships. If you choose not to
4 address this issue of financial relationships at
5 the beginning of your statement, it will not
6 preclude you from speaking.
7 The FDA and the committee places great
8 importance in the open public hearing process. The
9 insights and comments provided can help the agency
10 and this committee in their consideration of the
11 issues before them. That said, in many instances
12 and for many topics, there will be a variety of
13 opinions. One of our goals today is for the open
14 public hearing to be conducted in a fair and open
15 manner, where every participant is listened to
16 carefully and treated with dignity, courtesy, and
17 respect. Therefore, please speak only when
18 recognized by the chair. Thank you for your
19 cooperation.
20 We have 23 speakers who will be given three
21 minutes each. Will speaker number 1 step up to the
22 podium and introduce yourself? Please state your

name and any organization you are representing, for the record.

DR. BRINTON: My name is Eliot Brinton. I am reading a statement on behalf of Seth Baum.

"Members of the Endocrine and Metabolic Drugs Advisory Committee, thank you for giving me the opportunity to share my thoughts regarding an expanded indication for icosapent ethyl. I am immediate past president of the American Society for Preventive Cardiology, and although I am speaking today on my own and not on the society's behalf, this leadership position is highly relevant.

"The society's mission to promote the prevention of cardiovascular disease and advocate for the preservation of cardiovascular health has been my personal and professional goal for the last 20 years. Importantly, I spent the first part of my career almost exclusively treating, not preventing, cardiovascular disease. In cardiac catheterization laboratories, I tried to manage atherosclerosis long after its inception, often

during the throes of life-threatening and permanently devastating events.

"Recognizing the futility of this band-aid approach, I later turned my full attention to cardiovascular disease prevention, believing that with more strategic efforts on the part of clinicians and patients, combined with successful innovations by pharmaceutical companies, there would come a time when we would truly prevent the events that I had battled during my early years as a physician.

"Consistent with the tenets of the ASPC, I have maintained that heart attack, stroke, and even cardiovascular death can all be reduced or even averted. Rigorous research and development have indeed produced effective therapeutics. Unfortunately, costs has recently become an unexpected and unprecedented barrier to access for scientifically validated and FDA-approved therapies.

"This year in the U.S., over 1 million coronary events will occur, over $400 billion will

be spent on CVD, and 800,000 people suffer a stroke with 90 percent of these being considered avertable had proper preventive strategies been in place. No one can dispute the need for new therapeutics that can effectively decrease the burden of CVD in America. Similarly, we can no longer argue that the cost of treatment is irrelevant. Therefore, what we desperately need are effective and low-cost solutions.

"Icosapent ethyl satisfies both criteria. REDUCE-IT demonstrated highly statistically significant reductions in stroke, MI, coronary revascularizations, unstable angina, and cardiovascular death. Icosapent ethyl reduced these events while being safe and well tolerated. In addition to being effective, the drug was also deemed cost effective by the Institute for Clinical and Economic Review.

"ICER, historically critical of pharmaceutical pricing, acknowledged in its recent review of icosapent ethyl that the drug is highly cost effective with an incremental cost per

quality-adjusted life-year of $18,000 for the base case and $16,000 when revascularization and unstable angina were considered, in addition to Mi, stroke, and CV death.

"The valuation of icosapent ethyl is, therefore, far better than the often cited $50[000] to $150,000 per quality needed to demonstrate cost effectiveness. Thus, icosapent ethyl is precisely the therapeutic we want and need. It is a highly effective, safe, and inexpensive drug that can be used to reduce the risk associated with our most prevalent and costly health problem, cardiovascular disease.

"In sum, as an impassioned leader in preventive cardiology, I believe that the expanded indication for icosapent ethyl is a must."

DR. BURMAN: Thank you very much. I believe you're representing several people. Will speaker number 2 step up to the podium?

(Laughter.)

DR. BRINTON: Good. Yes, we've got slides. Thank you. This is on behalf of Professor Alberico

Catapano, a colleague and friend of mine from Italy.

"Thank you for allowing me to share my perspective. My name is Alberico Catapano. I'm a full professor of pharmacology at the University of Milano, director of the laboratory for the study of lipoproteins and atherosclerosis of the Lipid Clinic at the Bassini Hospital and of the Center of Epidemiology and Preventive Pharmacology of the University of Malano.

"Since 1972, I have been involved in the field of atherosclerosis, lipids, lipoproteins, and genetic dyslipidemias, and have authored more than 460 scientific papers in peer-reviewed journals on these topics. I am past president of the European Atherosclerosis Society; chairman of the EAS Educational Guidelines and Corporate Activities Committee; and chairman of EAS/ESC Guidelines for the treatment of dyslipoproteinemias.

"Please allow me to provide perspectives on why leading European societies in cardiology updated guidelines to include icosapent ethyl, even

1 though the agent is not yet commercially available
2 in Europe. Cardiovascular risk reduction and the
3 role of triglycerides and triglyceride recycle
4 proteins, such as VLDL and their remnants has been
5 an area of much focus. We've been trained to
6 measure and lower LDL to reduce cardiovascular
7 risk, however, a more comprehensive approach is
8 needed related to the role of all atherogenic
9 lipoproteins; that is ApoB-containing lipoproteins.
10 "Years of study of cardiovascular disease,
11 our need to understand the patient's full-risk
12 profile, and connection of residual risk of
13 dyslipidemia beyond LDL led the EAS/ESC guidelines
14 to recommend triglyceride testing as part of
15 routine lipid analysis with the same class and
16 level as LDL. Triglyceride-rich lipoproteins
17 should be reduced, especially in patients with
18 diabetes, metabolic syndrome, and elevated
19 triglyceride, and we have mandated secondary goals
20 such as non-HDL incidence patients.
21 "Use of Omega-3 fatty acids to correct
22 post-statin persistent atherogenic dyslipidemia is

an area of debate. On one hand, you have many failed trials studying low dose, 1 gram per day, EPA-DHA mixtures that do not affect plasma triglyceride. On the other, we have REDUCE-IT, studying a high dose, 4 grams per day, of an EPA-only agent, effectively reducing plasma TG and atherogenic lipoprotein burden and showing a 25 percent relative risk reduction in MACE in patients on optimal therapy, including statins.

"What happened with icosapent ethyl, a combination of the right population, with the right agent, and the right dose? Based on these unprecedented and consistently robust results, we recommend that in high-risk or above patients with triglycerides between 135 and 499, despite statin therapy, Omega-3 fatty acids, that icosapent ethyl 2 grams twice daily should be considered in combination with a statin.

"The validity and meaningfulness of data from this single REDUCE-IT trial was compelling and meaningful in addressing risk we recognize in many patients, both who have had an event and those who

1 are at very high risk of having their first. I
2 hope my comments are helpful in your decision, and
3 respectfully wish to thank you for the time to
4 present my opinion on this clinically relevant
5 topic."
6 DR. BURMAN: Dr. Brinton, thank you. Before
7 you step down, very quickly, please announce any
8 financial relationships you have or support for
9 coming to the meeting.
10 DR. BRINTON: I will do that right now. I
11 have travel support from Amarin to be here. I also
12 have received honoraria as a speaker and consultant
13 to them. I'm also a consultant to AstraZeneca, a
14 competitor of Amarin in this field. I have no
15 equity position in any of these companies.
16 DR. BURMAN: Thank you. Will the next
17 speaker step up to the podium, introduce yourself,
18 and note any potential conflicts?
19 DR. FOX-RAWLINGS: Thank you for the
20 opportunity to speak today on behalf of the
21 National Center for Health Research. I am
22 Dr. Stephanie Fox-Rawlings. Our center analyzes

scientific and medical data to provide objective health information to patients, health professionals, and policy makers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

Drugs to help reduce the cardiovascular events saves lives. The REDUCE-IT study provides encouraging data that AMR101 may help, but there are some important concerns that must be addressed before approval. Let me start by commending the sponsors for studying more than 8,000 patients for a medium of 4.9 years. Unfortunately, the sponsor provided only one phase 3 clinical trial studying MACE.

As we all know, replication is the key to scientific evidence. Independent clinical trials could have smaller or larger effects due to differences in patient demographics, comorbidities, as well as other factors. For example, there was a statistically significant effect for men but not for women. The trend was close to significant for women, but close doesn't count. Without a second

study, it's impossible to know if this treatment is effective for women.

We share FDA's concern that the placebo may have interacted with statin absorption because this could have affected the rate of cardiovascular events. While the FDA analysis suggested that the effect was estimated to be small, we can't know how completely the FDA was able to estimate all the ways this interaction could affect cardiovascular risk.

The mission of the FDA is to provide patients with real clinically meaningful benefits and that those benefits outweigh the risks. In this case, at least some patients taking the drug had an increased risk for adverse events like atrial fibrillation and atrial flutter or for bleeding. It is important that the reduction in the risk for cardiovascular events outweighs these risk for harm.

As advisors to the FDA, it is essential that you speak on behalf of patients' safety as you carefully consider the data available for how this

drug could help or harm patients. We agree with the FDA that the indication is too broad because it would include patients who were not studied in the phase 3 trial. If you believe that the FDA should grant approval, we respectfully urge you to limit the indication to a more appropriate population. Thank you.

DR. BURMAN: Thank you. Will the next speaker approach the podium and give any conflicts of interest?

MR. SHIRLEY: My name is David Shirley. Roughly six years ago, the question was asked of 11 advisory committee members in the same room if they thought there was sufficient evidence that Vascepa would lower cardiovascular events; 9 members voted against approving Vascepa and only 2 voted in favor. I must admit that I most likely would have voted right along with the other 9 because of the wording of the question and the limited studies available at that time, but I cringe to think how much unnecessary pain and suffering could have been eliminated had there been a vote that day.

Now though, that question has been answered with a resounding yes. Vascepa does lower cardiovascular events and even saves lives. My journey with Vascepa started years before the ADCOM, when I was out to prove that it was nothing more than a scam. I couldn't believe that anything derived from fish oil could prevent heart disease and that JELIS was a manipulated study run by dishonest researchers.

After many years of diligently studying the science of EPA, I came to know for myself that REDUCE-IT would be successful because science is governed by laws which must be obeyed. EPA has molecular laws which it, too, must follow when it is either acting or being acted upon, and these results are predictable. It doesn't have a choice whether it wants to follow the laws or not; it must.

That's why I love the incredible p-values in REDUCE-IT. Statistics protects us from making foolish interpretations and gives us confidence in our understanding. Some studies, however, are not

1 powered to give significant p-values, especially
2 when dealing with smaller subgroups or subsets.
3 That is where reason and common sense must be used.
4 Look at how the subgroup is studying and how it's
5 trending. Use past scientific experiences and lean
6 on the understanding of others with deeper
7 knowledge in these areas for direction.
8 Now, six years later, we have a significant
9 outcomes study that we can gain confidence from.
10 Have you thought about why you were chosen to sit
11 on this advisory committee at this time in history?
12 This is probably the most important advisory
13 committee that will be held over the next decade or
14 possibly longer. Your opinion will have huge
15 ramifications on how heart disease in the U.S. is
16 treated from this point on.
17 You're the pioneers. Your sacrifices and
18 knowledge have led you to this much deserved
19 privilege, and burden, on how to treat the number
20 one disease condition in the U.S. and the world.
21 Please be wise and err on the side of treating and
22 protecting individuals who may be at risk since

Vascepa has such an unusual safety profile.

Use the power statistics when appropriate, and when not, use reason, common sense, lean on your professional life experiences and the wisdom of others in your areas of expertise. And finally, realize that it's not the FDA or Amarin that you represent today; it's me. It's everyone behind me. It's your family. Basically, it's every American, whether they understand what cardiovascular disease is or not.

I have complete trust that you will do what is best for the American people and stop the delay in people getting the appropriate treatment. Thank you.

DR. BURMAN: Thank you. Will the next speaker come to the podium and note any conflicts of interest?

DR. BANSAL: I am a clinician practicing internal medicine in endocrinology since 1990, and I have my expenses paid for the travel by Amarin. I would like to present two cases to suggest these are two representative cases I've seen in my own

clinical practice, where I would suggest the use of the product in question today as recommended by the ADA in their standard of recommendations in March of 2019.

The first patient is a 60-year-old male. Since 2001, after his first myocardial infarction and at the age of 40, his risk factors included dyslipidemia, metabolic syndrome, smoking, and obesity. He was treated with ACE inhibitors, high-dose statins, antiplatelet drugs, and beta blockers, and gave up smoking.

By 2007, he had developed non-insulin dependent diabetes, which is currently treated with Metformin GLP-1 and an SGLT2 for an A1c of 6.5. His blood pressure is well controlled. He's treated with fibrates and Niaspan in the past. He continued to have recurrent episodes of obstructive coronary artery disease requiring hospitalizations and 5 stents.

Next slide, please. His current lipid profile shows a total cholesterol of 180, triglycerides of 380, HDL of 38 with a calculated

LDL of 70. After the REDUCE-IT trial, I recommended IPE, and his pharmacist manager advises him to use OTC fish oil due to cost and reviewing the package insert. His visit to the cardiologist, returned back, was not a fan of fish oil.

The second case, the next slide please, is a 48-year-old white male of Asian descent, non-insulin-dependent diabetes, non-smoker, sedentary, abdominal obesity, and family history of coronary artery disease. He's adequately controlled. His total cholesterol is 146, triglycerides are 280, and HDL is 39. Despite two appeals to the pharmacy managers, it is not approved as an indication.

Hence, just calculating in my clinical practice, I think I would save a hundred events a year, and I would therefore recommend that the FDA and the experts consider this as an adequate indication.

DR. BURMAN: Thank you. Would you state your name for the record? I apologize. I didn't ask earlier.

DR. BANSAL: Sorry. My name is Sudhir Bansal. I'm a clinical endocrinologist.

DR. BURMAN: Thank you. Will the next speaker walk up to the podium and state your name, any organization you are representing, and potential conflicts?

DR. D'AGOSTINO: Hi. Good afternoon. My name is Dr. Ronald D'Agostino. I am a clinical cardiologist. Thank you, EMDAC committee, for the opportunity to present my thoughts to you about approving a new drug application for Vascepa, icosapent ethyl. My disclaimer, Amarin has paid for my travel expenses to attend the meeting. In the past, I've received honoraria as a promotional speaker from Amarin for Vascepa, and I do have an equity position in the company. 19:55

I am a board certified internist and cardiologist and fellow of the American College of Cardiology and the American College of Physicians. I've been in practice since 1992. I hold academic positions at several university medical schools, and I'm affiliated with several university hospital

systems.

My primary goal is to safely take the very best care of my patients by encouraging a healthy and active lifestyle, and employing optimal medical treatments as appropriate and needed. To do so, I reached for professional guidelines, the medical literature, my own clinical experience, and to that of my trusted and esteemed colleagues.

Incorporating all of this input leads me to conclude, without any reservation or hesitation, that adding Vascepa to optimal medical therapy, including appropriate statin therapy, for patients who have even just mildly elevated triglyceride levels greater than 135 milligram per deciliter, and cardiovascular disease, or type 2 diabetes with just one additional cardiovascular risk factor, will significantly reduce their risk of having a major adverse cardiovascular event, MACE, and most importantly reduce their risk of a cardiovascular death.

I've been prescribing Vascepa for many years for my patients with hypertriglyceridemia and

established cardiovascular disease, or type 2 diabetes, with great success, and virtually no adverse side effects outside of occasional mild gastrointestinal upset or arthralgias.

You all well know the formidable Vascepa data, especially from the REDUCE-IT trial, which the New England Journal of Medicine Journal Watch praised as the single most important study of 2019. The ADA, NLA, NHA, and the European societies of cardiology and atherosclerosis have incorporated the REDUCE-IT findings into their guidelines.

Not since the introduction of statin therapy have we had such a profound addition to our important cardiovascular and lipid treatments. As you know, we have not seen cardiovascular benefit with the over-the-counter fish oil supplements, which are entirely different in variable products, and, unfortunately, many of our patients turn to these products, thinking that they are helpful, and many of my own patients turn to them when my prescribed Vascepa is not covered by their insurance plans.

So I respectfully ask that you advise the FDA to grant Vascepa a new drug application so that we may properly prescribe it to our appropriate patients with FDA approval, which will hopefully enable better access to it for our patients. Thank you for your attention.

DR. BURMAN: Thank you. Dr. Brinton, We welcome you back to the podium. Please state who you are representing and any potential conflicts, and your name.

DR. BRINTON: So this is Dr. Brinton. I'm representing Antonio M. Gotto, Jr. He did not state his conflicts, so I can't comment on that. But I will read his statement.

"I'm pleased to present to this open public hearing session. I have studied lipids, atherosclerosis, and CV disease for over 50 years. During this time, I have treated thousands of patients with dyslipidemia. I was a principal investigator in the coronary primary prevention trial and participated in many other lipid trials. I have served as the president of the American

Heart Association, the International Atherosclerosis Association, and the National Lipid Association.

"My opinions expressed in support of an FDA indication for reducing ASCVD with icosapent ethyl are personal. I do not speak on behalf of any organization, but I do feel I represent the 5-plus plus million Americans with ASCVD and diabetes with elevated triglycerides.

"These individuals are at high risk of a CV event despite optimal treatment with statins and LDL cholesterol levels below 100 milligrams per deciliter. This represents an unmet clinical need with no FDA approved effective therapy. Persons with diabetes are at especially high risk, and several treatment guidelines have classified diabetes as being a coronary heart disease equivalent.

"In my opinion, REDUCE-IT is a landmark study with a clinically significant reduction in CV events. No other study of subjects with diabetes or hypertriglyceridemia has ever shown such

dramatic results. I chaired the DSMB of the NIH-sponsored ACCORD study with thousands of diabetics, and as the father of two diabetic daughters, I have a personal knowledge of the CV ravages caused by this disease.

"Adding fenofibrate to baseline statin therapy resulted in no benefit in these diabetic subjects, whereas adding icosapent ethyl by diabetics and others with ASCVD in the REDUCE-IT trial led to a remarkable decrease in events. I strongly urge approval of icosapent ethyl to prevent ASCVD in patients with ASCVD, or diabetes with one other risk factor, and individuals on statin therapy with triglycerides greater than 135.

"The benefit greatly outweighs the risk and has the potential for decreasing pain and suffering in millions of patients. Thank you for allowing me to speak."

DR. BURMAN: Thank you. I wanted to mention that there is a clicker for any slides for any of the speakers, that's on the podium. We will invite our next speaker. Please state your name, the

organization you're representing, and any potential conflicts.

DR. BRINTON: I'm Dr. Eliot Brinton, president of Utah Lipid Center --

(Laughter.)

DR. BRINTON: -- at Salt Lake City, in case you didn't know who I was, and I want to tell you why I'm strongly in favor of this new indication, the proposed indication for icosapent ethyl. First of all, I've had the good fortune of being involved in lots of teaching opportunities around the country and various large meetings. But most relevant to today, lots of small group meetings. I've conducted more than 3,000 small group seminars, primarily on the subject of lipids; secondarily on the subject of diabetes, with more than 40,000 U.S. based clinicians.

I've also had the opportunity for a front row seat in guidelines from ACE. In LA, I was a reviewer for the REDUCE-IT statement that has been mentioned already. I'll mention it again later; past president of the American Board of Clinical

Lipidology, which is the only board certification entity for lipidologists; of AHA, I was a co-author of the scientific statement, which has been mentioned, and I'll mention it again, various other societies, and a steering committee member for REDUCE-IT.

Is there an unmet need? Yes. This was mentioned earlier, but let me just reiterate. This is a slide you've seen already. Randomized clinical trial data from this trial and other trials has shown that there is an excess risk despite aggressive statin therapy with triglycerides that remain elevated. Many observational studies in this one and others have shown the same finding.

Icosapent ethyl meets this unmet need. Mention has not yet been made about the paper that came out Monday of this week. We showed a decrease in total mortality in a U.S. population, a subgroup of REDUCE-IT, a prespecified endpoint. We also see something that's very relevant to the deliberations of the committee across risk factor subgroups'

consistency, including age.

Yes, the primary endpoint suggested a little bit of a difference, but in the key secondary endpoint, which is more robust in heart endpoints, there was no difference; also, no difference by age in the U.S. subpopulation of REDUCE-IT; no difference by age in JELIS; a 30 percent reduction in total events relevant to secondary prevention. In contrast, as has been stated, other triglyceride lowering treatments do not have those data.

So what about primary prevention? Very important, a key question I think for the committee; comparable CVD event reduction, no indication of heterogeneity whatsoever between primary and secondary. Why is this important? I do not want to have to tell my patients, "Sorry. I can't treat you until you have your heart attack. And then if you're still alive, come back, and I will treat you." That is not a good discussion to have. We have way too many sudden cardiac deaths, first heart attack, and as was shown earlier, 31 percent reduction of sudden cardiac deaths in

REDUCE-IT.

So does it meet this unmet need? Yes. This is a slide for the discussion of the presentation of REDUCE-IT, a DHA meeting showing icosapent ethyl added to that list of statin adjuncts proven to work, which my pointer or my slide advancer is not doing. Two guidelines [inaudible - mic off].

DR. BURMAN: Thank you. Will the next speaker come to the podium? State your name, any organization you're representing, and any conflicts.

DR. MASON: I'm not Eliot Brinton. I'm Preston Mason today --

(Laughter.)

DR. MASON: -- though he's a great guy.

I'm affiliated with Brigham and Women's Hospital and Lucid Research, though I was not involved with the REDUCE-IT trial. I have received consulting and research support from the applicant and other companies in this area. I'd like to discuss the importance of having a prescription product for treatment at the right formulation, the

right dose, and the right patients like in REDUCE-IT.

I recently was asked to speak for the American Heart Association on the role of dietary supplements. This is my disclosure for that particular presentation when it comes to dietary supplements. These are widely used, and there's a lot of confusion over their appropriateness. Many confuse them as FDA regulated OTC products, and their advertising would be very confusing to patients and consumers alike, promoting heart health and even prescription quality.

When in fact we did an analysis of what's in these dietary supplements, only about a third is Omega-3 fatty acid, a full third is saturated fat, and another third is other types of oils of unknown health benefits. If you isolate the dietary supplement, it's actually a solid at room temperature compared, of course, to a prescription product.

The reason also for the damaging effects of these is that they're highly oxidized, even

according to industry standards, and that's because they're a byproduct of an industrial process primarily designed to make protein feed. I don't know how this was justified, but they gave healthy subjects oxidized fish oil, and after a period of 7 weeks, there was a significant elevation in non-HDL cholesterol, LDL, and remnant cholesterol. So these are not a neutral effect but actually can promote dyslipidemia.

It's important because Omega-3 fatty acids like EPA are rapidly incorporated to lipoprotein particles. If they're not oxidized, they're very effective in protecting them from oxidation, as we and others have observed. We even see differences between EPA and other Omega-3 fatty acids with respect to this atheroprotective benefit.

Here, we're looking at oxidation over time and different ApoB-containing particles. You can see that only EPA was able to preserve LDL from oxidation compared to DHA or vehicle, and that's because even small changes in the number of carbons or double bonds can have very profound effects on

how these molecules interact with cells and lipoprotein particles.

So the conclusion is that fish oil supplements are not appropriate for patients for the reasons stated here. Thank you very much.

DR. BURMAN: Thank you. Will the next speaker come to the podium? State your name, any organization you're supporting, and any conflicts?

DR. UUSINARKAUS: My name is Kari Uusinarkaus, and I am a primary care physician in Colorado Springs. I'm also an adjunct assistant professor of family medicine at the University of Colorado. I did receive travel support from the applicant, as well as having spoken for them and an equity interest.

I have a busy primary care practice. I see 20 to 27 patients on a daily basis. As the data indicates, a lot of what I see is cardiovascular treatment or prevention. That is what I focus my practice on. I had a patient that came into my office about two weeks ago. We'll call him Joe. Joe is 52 years old, Hispanic. He has a sedentary

job. He's got two teenage children.

His chronic medical issues include diabetes, hypertension, dyslipidemia, and obesity. His medications include a high potency statin, blood pressure meds, including lisinopril and hydrochlorothiazide, and Metformin. His BMI is 35. His recent lipid profile showed a well-controlled LDL cholesterol of 90. His triglycerides remained elevated at 210.

I reviewed the REDUCE-IT data with my patient Joe. He sounded interested. I went ahead and prescribed icosapent ethyl, 2 grams BID. Shortly thereafter, I received a denial letter from the insurance company. I went ahead and filled out a prior authorization form, which took several minutes, and then I had my medical assistant submit it.

Several days later, I received another denial letter, so I requested a peer-to-peer, which had to be scheduled a few days in the future. When the day arrived, the physician on the other end happened to not even practice in the state that I

practiced in but was from New York. I asked her about covering icosapent ethyl for this patient, as he fit the criteria for REDUCE-IT perfectly. She had never heard of the REDUCE-IT data, so lovingly, I offered to send her a copy of the New England Journal article, which I did. It's two weeks later now, and I'm still waiting to hear back from the insurance company on the coverage for this agent.

So what I would appeal to the committee would be to look at the data. There are many, many patients that would benefit from it. I would like to prescribe the medication without the roadblocks that are currently in place for me being able to prescribe it. Thank you for your attention and consideration.

DR. BURMAN: Thank you. Will the next speaker come to the podium? State your name, any organization you are presenting, and potential conflicts.

MR. POLLNER: Hi. My name is Mark Pollner, and I'm a patient on Vascepa, and I have received travel support from Amarin. In 1996, at the age of

43, I had a heart attack and ended up with double bypass surgery. About 10 years later, I had a stent procedure. Imagine at such a young age with young children, a stay-at-home wife, many financial responsibilities, my career going well, and more importantly, so much to live for.

Fortunately, I recovered from my surgery and was back to work in 6 weeks, full time in 10 weeks. I changed my diet, began to exercise more, which became a family activity, and more importantly, my cardiologist put me on a regimen of medications to lower my cholesterol, heart rate, and triglycerides. My heart rate and triglycerides went down traumatically, but my triglycerides did not change much. I tried different fish oils and niacin, which I had some side effects from.

About a year ago, I was introduced to Vascepa. After a month, I saw my triglycerides decrease and I had no side effects. From what I have read over the recent months, Vascepa not only reduces triglycerides level but also has a profound effect on reducing the risk of a cardiovascular

event, especially if you're on a statin.

Personally, I think it behooves the medical, pharmaceutical, and insurance companies to change the parameters of this drug. Just think of the financial implications if we can lower the risk of cardiovascular events. I think the drug pays for itself in so many ways.

In closing, if there were more medicines to improve your health and decrease the risk of cardiovascular event, then they should be available to the public. All the data shows that Vascepa meets this criteria, so therefore it should be available to patients with a cardiac history whose triglycerides are above 135 milligrams per deciliter.

I can't stress enough how impactful having what happened to me, particularly at age 43, affected my family, friends, and colleagues. Obviously, if this can be avoided, it can make such a difference in people's lives. I would like to add that we are all looking to reduce healthcare costs. Isn't prescribing Vascepa cheaper than the

alternatives? Thank you.

DR. BURMAN: Thank you. Will the next speaker come to the podium? State your name, any organization you're representing, and potential conflicts.

DR. LUI: I'm Henry Lui from Jackson, Tennessee. Amarin is supporting my travel, but I am not being compensated for my time. This presentation is mine alone, representing myself as a concerned clinical practicing physician. In private practice for over 25 years, I am both a board certified interventional cardiologist and lipids specialist and a medical director of Research Associates of Jackson, one of the sites for the REDUCE-IT trial.

REDUCE-IT showed there was no difference in benefit between the lower and upper triglyceride tertiles, and Dr. Ann Marie Navar from Duke showed the risk for cardiovascular disease rises rapidly, even with low triglycerides below 150. In fact, the risk appears to start perhaps even at 50. Do we really know what a normal triglyceride level is

for Americans?

West Tennessee is one of the highest rates of both diabetes and cardiovascular disease in this country. For example, I currently have several patients who had bypass surgery in their late thirties, some being diabetic. They subsequently needed coronary stents a few years later before the age of 40 or at 40. I attempted to add icosapent ethyl after the REDUCE-IT trial resulted, but failed because the drug plants rejected its use because of the current label.

This is one of several similar situations in which access to this most needed drug is woefully inadequate. I am frustrated by drug plants who utilize stated labeling to withhold or assign high co-pays, making it cost prohibitive for patients. Resubmitting the denials also waste my time.

Can we reliably say patients on statins and unable to achieve LDL less than 100 be eligible for icosapent ethyl? Do we really need to tell a 40-year-old patient who had bypass surgery he or she is not eligible but will need to wait until age

45? Do diabetics at age 40 with 4 or more risk factors need to wait until age 50 or until they have their first event, which may of course be sudden death?

We treat patients, not numbers. By assigning an age, or a triglyceride number, or anything else other than simply to lower cardiovascular disease, morbidity, and mortality, the drug clans can limit access to this most needed drug for such a high=risk population. By reducing tens of thousands of cardiovascular related events per year, our society can truly benefit long term. Thank you.

DR. BURMAN: Thank you. Will the next speaker come to the podium? State your name, any organization you're representing, and potential conflicts.

MS. ROSS: Good afternoon. My name is Joyce Ross. I'm an independent nurse practitioner and clinical lipid specialist with greater than 23 years of clinical experience in the field of dyslipidemia and cardiovascular risk intervention,

with my clinical affiliation at the University of Pennsylvania and mostly with Dr. Daniel Rader.

I am past president of the national Association, as well as the Preventive Cardiovascular Nurses Association. I am not representing those organizations today; rather, I am participating independently as a concerned healthcare provider. In full transparency, please note that I have received travel assistance from Amarin for the meeting.

For greater than 100 years, cardiovascular disease has been shown to be the number one killer of the American population. In spite of huge advances in treatment modalities, many patients continue to experience cardiovascular events in the setting of well-controlled LDL cholesterol.

Needless to say, this is a major cause of disillusionment, both on the part of the patient and the healthcare provider. This type of recurrent crisis begs for proven affordable and accessible therapy to stop the bleeding. Healthcare providers are often frustrated with

regard to seeing patients with well-controlled LDL cholesterol, but triglycerides less than 500 going on to second, third, or even fourth events.

To date, we have no approved to treatment except lifestyle management and tighter control of diabetes, and other concomitant medical conditions. This creates a conundrum for the patient and the provider as well.

It is frustrating to have patients do what is recommended, such as exercise, diet, along with taking their medication, only to have further progression of their disease. The very worst conversation you will have with your patient or their family is when they look at you and say, after their second cardiac event, "What happened? I was doing everything you asked."

Research that has been recently produced with the REDUCE-IT reveals data is not just about cholesterol levels, but there are suggestions that other pleiotropic effects, and as you heard already today, about how this changes and informs clinical practice. The question, though, is who should be

1 treated?
2 John is a 66-year-old man, status post MI at
3 age 43, and is a second heart attack for him. He
4 had another one at 58. His BMI is 31,
5 hypertension, and he is a smoker, and he has
6 regular standard therapies. His LDL cholesterol
7 currently is 68 milligrams per deciliter and
8 triglycerides are 185 milligrams per deciliter. He
9 is not fully compliant with his lifestyle
10 management. The question is, what is a provider to
11 do?
12 Lifestyle management, smoke cessation, and
13 weight loss and regular exercise, of course, are
14 the most important things to start with. But what
15 about this gentlemen? 68 milligrams per deciliter
16 for LDL -- I'm done? [Inaudible - mic off].
17 DR. BURMAN: I'm sorry. The time has
18 expired, but I think we got your message and
19 appreciate your comments. Thank you for coming
20 down.
21 Could we have the next speaker come to the
22 podium? Note your name or any organization you're

representing, and your potential conflicts.

MS. KELLY: Good afternoon. My name is Taylor Kelly, and I serve as a policy advisor to Aimed Alliance, a 501(c)(3) nonprofit health policy organization that works to protect and enhance the rights of healthcare consumers and providers. Our funders are listed on our website@aimedalliance.org/alliance members, which include Amarin.

On behalf of Aimed Alliance, thank you for the opportunity to provide the patient perspective regarding why the FDA should approve Vascepa's pending supplemental NDA to reduce the risk of cardiovascular events as an adjunct to statin therapy in adult patients with elevated triglyceride levels.

As you know, Vascepa is already FDA approved to reduce triglyceride levels in adult patients with severe hypertriglyceridemia. Additionally, Vascepa has been shown to reduce the risk of cardiovascular events when used in combination with statin therapy in adult patients with elevated

triglyceride levels.

While a healthcare practitioner can currently choose to prescribe Vascepa to reduce such risk, the practitioner would be prescribing off-label. Private health plans are not required to cover an off-label use of an FDA-approved drug. When plans do cover off-label therapies, such coverage is often contingent on benefit utilization management policies such as prior authorization.

Prior authorization policies require a healthcare provider or a patient to obtain approval from the health plan before it will cover the cost of a treatment or medical service. This practice can delay access to life-saving treatments, interfere with the patient/practitioner relationship, and can be applied in a manner that is inconsistent with sound scientific evidence.

According to a recent study, off-label use is the most common reason for prior authorization denials. Consequently, we are hopeful that the approval of Vascepa for the additional indication of reducing the risk of cardiovascular events may

improve access to this treatment without burdensome benefit utilization management requirements.

Vascepa also provides significant value for cardiovascular patients as an FDA-approved prescription EPA Omega-3 fatty acid treatment. Currently, there are many dietary supplements that contain Omega-3 fatty acids, however, dietary supplements are not intended to treat medical conditions. They are not required to satisfy the rigorous FDA requirements that ensure safety and efficacy before they go to market. They may lack uniform doses, contain contaminants, or even lack the active ingredient. As such, dietary supplements can be unreliable, and in some cases dangerous.

An unreliable and ineffective dietary supplement may not work as intended and leave the patient's condition untreated, which may result in disease progression. This is particularly troubling for cardiovascular patients for whom the use of an ineffective dietary supplement may result in heart attack or stroke.

Consequently, an FDA-approved prescription Omega-3 fatty acid product to reduce the risk of cardiovascular events can improve health outcomes for this patient population by providing a consistent, safe, and effective option to lower elevated triglyceride levels. As such, Aimed Alliance recommends that the FDA approve the supplemental NDA for Vascepa. Thank you again for the opportunity to speak today.

DR. BURMAN: Thank you. Will the next speaker come to the podium? State your name, any company you're representing, and potential conflicts.

DR. GOODMAN: Thank you for giving me this opportunity to speak to explain my personal experiences with Vascepa. I have not accepted any compensation from Amarin. I am an 85-year-old retired ophthalmologist. I practiced medicine for over 40 years. During this time, I taught residents and students at Harvard, Tufts, and BU Medical School. I was an associate clinical professor at Boston University Medical School.

I have experienced 5 separate cardiovascular events, including 3 heart attacks and 2 strokes. I realize I'm at high risk for another cardiovascular event even though I've maintained normal triglycerides over the years. I believe that because I've been able to take Vascepa starting in 2017, I've had no cardiovascular events since then.

I experienced my first heart attack in 2001 and had my first stent implant at that time. I was prescribed Lipitor and had been taking it ever since. This first heart attack was followed by two more in 2003 and 2017, with two more stents being implanted. In addition, I had 2 strokes in 2006 and 2011. My cardiologist, however, continued to refuse to prescribe Vascepa because my triglycerides were normal. However, having had 2 strokes, I was also under the care of a neurologist.

In 2017, my neurologist agreed to prescribe Vascepa for me, and I've been using Vascepa ever since, and have had no cardiovascular events since starting Vascepa. In 2018, my cardiologist learned

the results of REDUCE-IT. He finally agreed to prescribe Vascepa. He was impressed with the fact that even the patients with normal triglycerides were found to benefit from the reduction of cardiovascular events after using Vascepa.

I presently understand that while Vascepa's effectiveness in reducing triglycerides is important, even more important is its effectiveness in reducing inflammation for all patients. Thank you.

DR. BURMAN: Thank you. Please state your name -- I'm sorry -- for the record.

DR. GOODMAN: My name is Edward Goodman.

DR. BURMAN: Say it again, please.

DR. GOODMAN: Edward Goodman.

DR. BURMAN: Thank you very much.

DR. GOODMAN: Thank you.

DR. BURMAN: Will the next speaker come to the podium? State your name, any organization you're representing, and potential conflicts.

MS. NORTON: Good afternoon. My name is Anna Norton, and I serve as CEO of DiabetesSisters,

a national nonprofit organization whose mission is to provide support and education to women living with or at risk of diabetes.

Our community consists of thousands of women of varying ages, ethnicities, and types of diabetes. We have even introduced an educational programming serving underserved populations to focus on African American, Latino, and Asian communities. Personally, I am a woman of color and have lived with diabetes for over 26 years. I have also received travel assistance from Amarin to be here today.

We know that people with diabetes have a multitude of challenges to their health, including risk of retinopathy, neuropathy, and neurology. Specifically, women with diabetes are at an increased risk of developing cardiovascular obstacles in their lifetime with heart-related challenges at the forefront of their health complications. We also know that, unfortunately, women as a whole are underserved and undertreated when it comes to cardiovascular disease.

It is imperative to educate and share information on the use of various therapies to aid in the prevention of complications over time and offer a proactive and upstream approach for better health outcomes. This approach must include education to better understand the relationship between diabetes and heart disease, and the heightened risk of heart attack, stroke, and death. Additionally, diabetes education should include information on cholesterol and triglycerides, and how both contribute to cardiovascular risk.

Statins have proven useful in facilitating treatment to decrease risk in people with diabetes and heart disease, but we're still missing a significant piece of the problem. A proactive approach by all of us can have a tremendous impact for people with diabetes, and specifically women who are naturally at risk for heart disease, and even more so for minority women who are at an even higher disadvantage.

The use Vascepa within the DiabetesSisters community can be beneficial to our overall and

long-term health. As we seek prevention and treatment for cardiovascular challenges as we walk our diabetes journey, we look for solutions to mitigate our possible complications and enhance our personal and professional goals. We support the use of this therapy to reduce cardiovascular risk to aid in successful and long-term health outcomes.

As a patient myself, and speaking on behalf of women with diabetes, I urge your approval of additional options to reduce our cardiovascular risk. Thank you for your time and consideration.

DR. BURMAN: Thank you. Will the next speaker come to the podium? State your name, any organization you're representing, and your conflicts of interest.

DR. WEINTRAUB: Good afternoon. My name is William Weintraub. I'm director of outcomes research at MedStar Washington Hospital Center and Georgetown University; professor emeritus of medicine and of public health at Emory university. My conflicts, I have grants from Amarin and consulting for Amarin, and they paid for my car

fare here today.

I'm going to posit to you that icosapent ethyl provides good value. I'm going to mention three studies in that regard. The first is a study that we did and published in the Journal of Clinical Lipidology last year. We looked at the cost of cardiovascular events using data from Optum Health.

Using regression analysis, we found that the additional cost for people with atherosclerotic vascular disease and of hypertriglyceridemia was just under $2,000 a year. We used data from NHANES to look at the societal burden, and using a rather narrow definition, there were over 6 million people who would be eligible. Total healthcare costs to the healthcare system, then, is the order of $12 billion a year. We think that's actually an underestimation. Societal burden of hypertriglyceridemia, even narrowly defined, is relatively high.

The next study I want to quote, you've already heard a little bit about this afternoon

already, and that's the ICER study. They looked at the cost effectiveness of treating patients in the REDUCE-IT trial with icosapent ethyl. They used the event rates in the trial, so they only used published data.

The other thing they did in that study was they looked at the cost of Vascepa, and they did this correctly, I believe, using net cost from SSR Health. The cost was just $4 and 44 cents a day. Thirty percent reduction in total events, $4 and 44 cents a day, this is really remarkable. Having worked in this kind of field now for 40 years, I've never really seen anything else quite like this. I think it's unusual and very important.

So what did they find? The incremental cost effectiveness ratio you've already heard is in the order of $17,000 for quality adjusted life-year gained, well within any societal estimation of value. I will be presenting patient-level data from the REDUCE-IT trial on Saturday morning. We found similar results.

I will summarize it to say, quite simply,

that we're very close to cost neutral; perhaps in some populations even cost saving, while reducing event rates at 30 percent. Vascepa provides great value, and I do hope that you will approve its use today. Thank you so very much.

DR. BURMAN: Thank you. Will the next speaker come to the podium? State your name, any potential organization you're supporting, and potential contracts.

MR. SCHATZMAN: My name is Bill Schatzman. I'm the patient that you're all hearing about. Vascepa, or Amarin, is paying for me to drive from Baltimore to here. That's all they're giving me. My story begins in my early twenties when I found out that I had extremely high cholesterol, and I was given statins. Immediately, I found out that I'm allergic to statins, and they make me extremely ill, and almost caused my death.

So where do we go from there? Well, I'm a young man, and it's the early '90s, and nobody's even talking about triglycerides at that time. They do diet, they talk about exercise, and over

the next years, I work very closely with my doctor. I become a vegetarian for 2 years with no effect. I ate oatmeal for 4 years every single morning. I tried things that were known to help like red rice, yeast, fish oil pills, no red meat, eating lots of fish. I hate fish.

(Laughter.)

MR. SCHATZMAN: Zero cholesterol diets. Natural pharmaceutical items never seemed to work. My doctor was diligent, and we tried new things as they were approved. But living in the southwest, eating fish is kind of difficult anyway, because I was from New Mexico.

Exercise and weight maintenance did little to help my numbers. To give you an idea of what kind of exercise I did, I was a bicycle police officer for a city police force in southern New Mexico in the desert. No effect. I was a SWAT team member, and I was also a gang task force member. I also joined the border patrol after that; still no effect.

I believe I had my first heart attack in

2010 when I was 45. I remember the doctor sending my blood to the laboratory to be evaluated, and the laboratory sent a note back, "Quit messing around." The doctor was extremely upset. He took the blood back himself, and my blood was so thick that it was difficult for them to run the tests. And when put in the centrifuge, my blood did not separate like normal people's do.

The doctor did not get the test results to determine whether I had had a heart attack or not, but I believe I did. The thickness of the clots [indiscernible] made it too difficult for the laboratory technician to get accurate readings. A heart cath in 2010 showed no significant blockages at that time.

Fast forward a few years, change in locations. In 2016, I had a heart attack while at work here in Washington, D.C. I didn't understand the symptoms well, so I didn't go to the hospital. Then, I had a larger heart attack at home. This is emotional for me, guys. I was told at that time I had high triglycerides, 3500 was my number. They

didn't have a problem in Baltimore hospitals figuring that out.

Between my triglycerides and my high cholesterol, the doctor was having a difficult -- no. Sorry. I lost my spot. After the larger heart attack and having been on Zetia, statins, niacin, and other medications, there was one other complication that I had. After having a heart attack, I was fired from my job as a government contractor. [Mic off].

DR. BURMAN: I'm sorry. Your microphone stopped because of the time, but because of your particular situation, we're happy to give you another 30 seconds.

MR. SCHATZMAN: I appreciate that.

My doctor tried to get Vascepa, but my insurance would not pay for it. I followed my diet. I worked out. I did everything I could, but one day I needed nitroglycerin to do my exercises. Two weeks later, I was taken 2 nitroglycerins to finish my exercise. I asked what was wrong. Two weeks later, I was in the hospital at 54 having

open heart surgery, a very scary time for me. Now I find out that Vascepa was available, but my insurance said no. My doctor said yes, but my insurance said no because I didn't fit their profile.

You need to change this. You are the body that can save patients like me and our lives. [Inaudible - mic off].

DR. BURMAN: Thank you.

MR. SCHATZMAN: You represent us.

DR. BURMAN: Thank you.

(Applause.)

DR. BURMAN: Thank you very much. Will the next speaker step up to the podium? State your name, any support you have, as well as any potential conflicts.

MR. CLYMER: Dr. Burman and members of the committee, thank you for the opportunity to address you today. I am John Clymer, executive director of the National Forum for Heart Disease and Stroke Prevention, a nonprofit coalition of organizations dedicated to preventing heart attacks and strokes,

1 and eliminating cardiovascular health disparities.
2 Amarin, the FDA, and several other HHS agencies are
3 among the more than 100 members of the National
4 Forum who are drawn from the public, private, and
5 nonprofit sectors. I have not received any
6 financial benefit from the sponsors.
7 The National Forum co-leads the Million
8 Hearts collaboration and convenes the Value and
9 Access Steering Committee. The latter is composed
10 of leaders of groups representing patients,
11 providers, public health, payers, and pharma and
12 biotech. It has developed a consensus goal to
13 enhance health and wellbeing by improving people's
14 access to evidence-based care that is appropriate
15 for them.
16 CDC estimates that 80 percent of premature
17 heart disease and strokes are preventable. The
18 Department of Health and Human Services' Million
19 Hearts initiative has drawn attention to this huge
20 opportunity to reduce the burden and premature
21 deaths caused by cardiovascular disease.
22 If we are to reach the Million Hearts goal

of preventing 1 million heart attacks and strokes by 2022, we must help people control risk factors, including high triglycerides. For some people, the array of medical and nonmedical therapies available today are insufficient to control high triglycerides. We just heard very compelling testimony to that effect.

Thus, most members of the Value and Access Steering Committee applaud the development of icosapent ethyl, which the REDUCE-IT trial found to control triglycerides and reduce risk for heart attack, strokes, and cardiovascular death. The committee has stated that icosapent ethyl confers gains in quality-adjusted survival and overall survival over optimal medical management. The committee notes that a cost effectiveness analysis by ICER found that costs for treatment with icosapent ethyl would fall below commonly cited thresholds for cost-effectiveness.

We are optimistic that the risk of heart disease in the U.S. can be reduced through safe and effective new treatment options such as icosapent

ethyl in combination with behavioral, educational, and other important initiatives and efforts, and that these therapies will help bring us closer to achieving the Million Hearts goal of preventing heart attacks and strokes.

200,000 preventable heart attacks and the human and economic burdens linked to them is an urgent reality that calls for urgent action; in this case, expanding the indication for icosapent ethyl.

DR. BURMAN: Thank you. Will the next speaker come to the podium? State your name, any organization you're representing, and potential conflicts.

DR. BUDOFF: Thank you very much for the opportunity. My name is Matthew Budoff. I'm a professor of medicine at UCLA. My conflicts are listed on my slide. I receive research funding from Amarin, as well as on the Speakers Bureau. They are paying for my taxi ride here, as I'm here on behalf of the NIH, chairing a summit today for them, so they paid for the 4-mile trip.

1 People have talked about the need for
2 replication, and I think we've already achieved
3 that quite well with fish oils and different
4 supplements. There have been 5 consecutive
5 negative trials using a mixture of DHA and EPA with
6 outcomes, and as you can see, 2 consecutive
7 negative trials looking at progression of
8 atherosclerosis as a mechanistic benefit. So we
9 now have 7 trials that are concordant showing no
10 benefit by combination use of DHA plus EPA.
11 Conversely, we have 2 positive trials with
12 EPA: for outcomes, the JELIS trial, resulting in a
13 19 percent reduction of events; and the REDUCE-IT
14 trial, demonstrating a 25 percent reduction in
15 events; and 6 trials looking at the mechanistic
16 benefit of EPA, all of which showed significant
17 benefit. So we have excellent replication, both
18 from a mechanistic standpoint, as well as from an
19 outcomes standpoint.
20 To further validate this, I am conducting
21 the EVAPORATE trial, a prospective randomized trial
22 that will be presented. It's embargoed until

Monday, as I'm presenting it in Philadelphia as a late-breaking clinical trial at the American Heart Association, but we will be looking at the mechanistic benefit of EPA versus placebo. The reason I point this trial out is because what is not embargoed is data that we've already presented, is data on the mineral oil and the concerns thereof.

We looked at the rates of progression with mineral oil and compared it to a matched cohort of patients who are on a cellulose-based placebo in another randomized prospective trial. I want to point out both of these studies were prospective, double-blind, placebo-controlled trials, and what we compare here is just the rates of placebo and progression across both trials. What you can see is exactly the same rates of atherosclerosis progression in those patients taking mineral oil, 4 grams as per the placebo arm of EVAPORATE, similar to the placebo arm of REDUCE-IT, as taking a cellulose-based placebo in another trial.

We looked at total plaque, we looked at

1 noncalcified plaque, we looked at every possible
2 metric of plaque, and these are identical -- [mic
3 off].
4 DR. BURMAN: Thank you very much.
5 Will the next speaker come to the podium?
6 State your name, the organization you're
7 representing, and potential conflicts.
8 MS. PEREZ: Hello. Good afternoon. My name
9 is Robyn Perez, and I am the manager of continuing
10 medical education at Taking Control of your
11 Diabetes. Please note that I have received travel
12 support from Amarin, and then I am here on behalf
13 of Dr. Steven Edelman.
14 Dr. Edelman is an endocrinologist and
15 clinical professor of medicine at the University of
16 California San Diego, as well as a VA medical
17 center. He is the founder and director of Taking
18 Control of Your Diabetes, a 501(c)(3),
19 not-for-profit organization, whose mission is to
20 educate and motivate people living with diabetes
21 and their loved ones, to live healthier, happier,
22 and more productive lives. Dr. Edelman sends his

regrets for not being able to be here today and has no relevant disclosures.

Although a major part of my career has been involved in clinical research in the type 2 diabetes space, my comments today are primarily focused on the clinical care aspect. People living with type 2 diabetes make up the primary bulk of patients in our clinics and the thousands of people I interact with at are Taking Control of Your Diabetes conferences held across the country every year.

By this time of day, you have heard a lot of data on Vascepa and statistics on the staggering rate of heart disease in people with type 2 diabetes. This is not a new finding. Elliot Joslin wrote about this dangerous relationship decades ago, and the recent cardiovascular outcome trials have now attracted new attention to this problem.

The most common cause of death in people with type 2 diabetes is not eye disease, it is not kidney dysfunction, it is not central or peripheral

neuropathy. It is heart disease. Much of our attention has been focused on LDL-lowering drugs, including the statins and PCSK9 inhibitors, however, elevated triglycerides have become a forgotten risk factor. The high triglyceride, low HDL relationship, along with treatment-resistant hypertension, central obesity, and a hypercoagulable state are the hallmark features of the metabolic syndrome contributing to the high rate of heart disease.

We need safe, effective, and especially well-tolerated therapies, and based on the data we've seen today, Vascepa is clearly one of them. The impressive clinical benefits of this medication far outweigh any potential risks. Adherence and persistence of type 2 medications, including cardiovascular risk reduction therapies, are extremely poor, which is why education to the individuals at risk is so, so important.

With concern for the millions of people living with type 2 diabetes in our country, I hope that you will vote to give Vascepa the status it

deserves. There still remain many urgent needs for this age-old problem and this high-risk population. Thank you so much for your time and attention.

DR. BURMAN: Thank you. Will the next speaker come to the podium? State your name, the organization you're representing, and any potential conflicts.

MS. BAER: Hello. My name is Andrew Baer, and I am the executive director for Mended Hearts. Our mission is to inspire hope and improve the quality of life of heart patients through ongoing peer-to-peer support, education, and advocacy. I appreciate the time to speak with you today.

I would like to disclose up front that I am receiving travel support from Amarin to attend this meeting on behalf of patients. I represent the largest cardiovascular peer-to-peer support organization in the nation. My comments today are made on behalf of the board of directors, our 29,000 members, and the millions of heart patients that we serve.

Cardiovascular disease is the number one

killer of Americans and carries an extremely high burden, not only financially, but emotionally and socioeconomically. Cardiovascular disease is chronic and lifelong, which adds to the burden of care for this disease.

Mended Hearts strives to bring equal access to life-saving treatments to all patients. We firmly believe that patients should have access to evidence-based, cost-effective treatments that are determined appropriate in consultation with their treating clinicians. We know that icosapent ethyl is already FDA approved and has been proven safe for patients.

This treatment is already reducing the risk of major cardiovascular events, and we believe that expanding the label for use in patients will allow a greater number of patients to receive this benefit. This could mean one less stroke, one less hospitalization, and one less time or less time away from their job. And to a family who is already managing a chronic illness, these steps are huge.

If the FDA will expand the use of this medication, physicians will have one more tool in their toolbox when working to improve the quality of life to patients. Despite the progress made in the cardiovascular world, we still see large disparities in women, in different ethnic groups, and in areas that are underserved socioeconomically. Mended Hearts believes that some of these individuals are less likely to have the resources to fight with insurance companies or even have insurance in some cases.

Vascepa is a cost-effective, safe treatment that could be offered in some treatment plans to help combat the chronic condition that our population faces. Reducing residual cardiovascular risk in statin-managed patients with elevated triglycerides and other risk factors of cardiovascular disease could improve the quality of life to hundreds of thousands of patients. This would not only improve the quality of life for the patients and their families, but would also reduce the risk of the overall hospitalization and

healthcare costs.

I appreciate your time for the comments today, and I would like to urge the FDA to approve the secondary indication.

DR. BURMAN: Thank you. Will the last speaker come to the podium? State your name, any organization you're representing, and potential conflicts.

DR. SHETH: Thank you for allowing me this opportunity to speak to you this afternoon. My name is Dr. Neil Sheth, and I'm a board certified lipidologist, family medicine physician, and a clinical researcher. I'm here today on my own accord, and I've received travel assistance from Amarin.

I want to address cardiovascular disease and how it impacts my patients and my practice. As you know, cardiovascular disease is the leading cause of death in the United States. In patients that have diabetes, that risk of death from cardiovascular disease is 2 to 4 times higher, and over 70 percent of people over the age of 65 with

diabetes will die from some form of heart disease or stroke.

That being said, cardiovascular disease prevention has been my primary focus of my practice over the last 11 years. In my clinical practice, I've always tried to follow the current guidelines to cardiovascular disease in my patients. After optimizing statins and other medications to control LDL, there still remains a very large residual risk of cardiovascular events.

There's an unmet need to add to our arsenal of therapies to reduce this residual risk. Many medications to reduce triglycerides, such as gemfibrozil and niacine, are no longer recommended by the FDA to be used in conjunction with statins due to safety concerns. As you have seen through the data from the REDUCE-IT trial, Vascepa can significantly help reduce this residual risk and can safely be used with statins.

Many guidelines and scientific statements by clinician societies, such as the American Diabetic Association, American Heart Association, and

National Lipid Association have updated their recommendations and specifically name icosapent ethyl to be used in high-risk patients with statin therapy. The guidelines go on to state that, quote, "The REDUCE-IT trial data should not be extrapolated to other products."

When looking at the REDUCE-IT trial, the patients involved in the trial closely mimic what an average patient actually looks like within my practice. With the way the medication is currently labeled, a very large issue that we're seeing in the real world of clinical medicine is that the insurance carriers have been denying access to the medication.

It's very frustrating to the providers, and patients alike, that when we as clinicians apply the clinical data to reduce both heart attack and stroke and prescribe according to the guidelines, this medication is still being denied for patient use. This does not benefit our patients and may actually cause more harm than good when our patients are then forced to use other Omega-3 fatty

acids that have not been shown to have any clinical benefit.

We now have a proven therapy that's safe, efficacious, and reduces mortality to fit this unmet need and reduce residual risk. After reviewing the data, I truly hope the FDA relabels this medication to reflect the current data and guidelines for the safety and wellbeing of my patients. Thank you.

Clarifying Questions (continued)

DR. BURMAN: Thank you, and thank you to all speakers. The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to the task at hand with careful consideration of the data.

The schedule calls for us to have comments on questions and discussion with the committee, however, there is some business left over from this morning. Obviously, there is a lot of work to do and barely enough time to do it, so I'm going to propose the following schedule: we'd invite the

FDA up first to answer any residual questions from this morning, then we'll invite the sponsor up to answer any residual questions from this morning as well.

There may be time for a couple of leftover questions for the sponsor or the FDA, but we're only going to have from 2:20 to 2:40 for this session, and then we will spend a half an hour on each question, questions 1, 2, and 3, and then spend time on the voting question.

So I hope that meets your approval. Does the FDA have any response to any lingering issues from this morning?

DR. SHARRETTS: [Inaudible - off mic].

DR. BURMAN: Please, Dr. Sharretts?

DR. SHARRETTS: Sorry. I forgot my microphone. This is John Sharretts. We have a few slides to answer some of the residual questions from this morning. If I can have slide 16 from my revised deck.

(Pause.)

DR. SHARRETTS: I'll start speaking while

we're waiting. This regards the question about the background anti thrombotics. I'm going to show you two different tables. The first one is an analysis by baseline antithrombotic use. What I wanted to point out is the limitation of that analysis, even though it's essentially like an ITT analysis, it doesn't reflect what the patients were actually taking at the time they had the event.

One important factor when we looked at the data is that a lot of people at the time of the event were receiving parenteral medications that are given at the time of cardiovascular procedures, like heparins, eptifibatide, bivalirudin, drugs like that. So the second analysis that you're going to see is an on-treatment analysis.

Now, there are challenges in looking at an on-treatment analysis because you're introducing a post-randomization variable into the data, and maybe that affects the numbers. But I think what you'll find is that the data are pretty similar for the two tables or at least the overall direction of the data.

Sixteen. As I was saying, this is the data for all randomized patients. You'll recognize the numbers are similar, that patients on no antithrombotics was 45; patients with bleeding versus 42. I think there's a slight difference between our numbers and the sponsor because when we did our analysis, we excluded people who are taking PRN pain medications that contain aspirin, from the subset of aspirin, but as you see, there's an increased risk of bleeding for the most common medications, aspirin, clopidogrel, warfarin.

As you go down the list, you see some of them trend the other way, but then I caution that the numbers are very small. As you see ticagrelor, it's 3 bleeds versus 7; prasugrel, eight please versus 12. So I think it's hard to draw conclusions about those numbers because the numbers are small.

If I can go to slide 18, this is the on-treatment analysis. I think the big difference that you notice on this is that the number of patients who qualify as no antithrombotic is

smaller. The applicant did this analysis for us, and they excluded not only patients who were on other oral antithrombotics; they were able to exclude all patients who were on parenteral antithrombotics.

Maybe you can flip to slide 19 for a second. I'll come back to this one so you can see the data. But as you see item 1, it excludes patients on all these drugs, so it's a little bit more reflective of people who are actually on no antithrombotic. The other thing talks about all the different names that we tried to combine to make sure that we got drugs in the right categories.

Now, can we go back to 18? This is the on-treatment analysis. Again, you see the same trends: aspirin, clopidogrel, warfarin; there's 20 to 30 percent more bleeding on the AMR101 arm than on the placebo arm.

DR. BURMAN: John, do you have anything further?

DR. SHARRETTS: The one other piece I have is a one-liner.

DR. BURMAN: Before you do that, Dr. Wilson has a very quick question.

DR. SHARRETTS: Sure.

DR. WILSON: So if you combine -- that's where I was going -- all of the orals, one or more orals and/or warfarin, as Dr. Konstam -- you're going to get close to a 2 percent delta at least. That top number is significant, as shown by the sponsor at 0.006, and I think if you reduce that, it's probably going to be between 0.01 and 0.05. If you add persons on one or more oral anticoagulants, like NOACs or on warfarin -- I mean, I'm just reading between the lines, adding up those numbers; so not looking at individual drugs but looking at all anticoagulation, or warfarin, or NOACs.

DR. SHARRETTS: Yes. We did not do inferential statistics on this because of the type of data it is. This is from an adverse event database, where the data is collected by just questioning, and the patients give the information. So there isn't systematic accumulation of the data,

and there isn't any adjudication of the data. So we can't do like a time-to-event analysis, and we can't necessarily do a model to do a time-to-event analysis.

DR. BURMAN: Dr. Sharretts, thank you. You had a second point that you're going to be real quick about?

DR. SHARRETTS: Yes. The last point is very brief, slide 20. Someone asked about the change in hemoglobin A1c over time, and there it is. It was a very minimal change from baseline to final visit and similar in both arms.

DR. BURMAN: You're right. It's very quick and very easy to see. Thank you.

For the sponsor, do you have a couple of issues that were brought up this morning you wanted to answer or address? Quickly and succinctly, please.

DR. JULIANO: Yes. Thank you. I'll start with the question around the interim analysis and whether or not -- I believe it was Dr. Ellenberg who asked -- we had achieved or surpassed the

statistical boundaries for the interim analyses.

The short answer is yes, and I can show you what those boundaries were in just a minute. But I think it's important to remember the backdrop that this study was conducted on. First, we were coming into a backdrop of a sea of failed Omega-3 studies. The only one that stood out was the JELIS study, and it had a number of design caveats that were brought up in multiple forums.

In addition, we knew that this study would be supporting a cardiovascular risk reduction as a single study and a new indication, so it was important that the data set was complete and fulsome. So it wasn't just the surpassing of the p-value for the primary endpoint that was taken into consideration by the DMC who conducted the two interim analyses.

Prespecified before the interim analyses, of course, they did look at the p-value for the primary, but they also looked for consistency across the key secondary endpoint, all of the other secondary endpoints, and also, in particular,

within subgroups. Because if you don't have a full data set, it's difficult to tell what's happening in the subgroups. And also, on the backdrop of not quite understanding if triglycerides mattered or not, subgroups such as those were important.

In hindsight, after unblinding -- of course, Amarin was blinded to all of this at the time, but after unblinding, we learned from the DMC that the primary prevention subgroups were just starting to separate quite late -- the subgroup was just starting to separate late. So there were things such as that primary prevention subgroup, total mortality had not been achieved, and then, of course, you want a fulsome safety data set.

I think statisticians among us could speak much better than I could. There are some concerns with overestimation of the effect if you stop early. So I think with all of those considerations in place, it's important to remember that the DMC had a prespecified algorithm to look through for all of those levels of consistency, and the DMC chose to continue to study. And frankly, we're

happy that they did, to give it a full data set.

But to actually answer your question, if I can pull up slide 3, this shows you the efficacy boundaries that needed to be achieved at the first interim analysis, IA number 1, the second interim analysis, IA, number 2, and the final interim analysis, you can see it as a one-sided or a two-sided alpha.

You can see for the final analysis, the spend for the first two analyses brought the p-value needing to exceed 0.034; the first interim, 0.0071 and the second interim 0.0177. And as I said, we did surpass those.

DR. ELLENBERG: So you said they surpassed them, but the board chose not to recommend early.

DR. JULIANO: Exactly. We surpassed them, and the DMC made the decision to continue essentially for a full data set.

There was another question that has come up a number of times around the committee, and especially Dr. Konstam suggested some difficulty in trying to understand or how to consider the mineral

oil effect and biomarker changes. If I can start by showing a covariate adjusted analysis that was within the briefing book, the appendix of the briefing book that we provided, and frankly, it's quite similar -- slide 2 up -- to the analyses conducted by the FDA.

At a high level -- I won't walk through all of it -- these are essentially analyses where you take into account the difference of a biomarker across the two treatment arms, essentially negate any benefit from that, and then ask how does it change the hazard ratio. So you want to compare each of the hazard ratios in the second column to .752, the hazard ratio observed for the primary endpoint.

If we take, for example, the LDL cholesterol derived value, which is the second value, you see that there is not a substantial difference. And frankly, across all of these values, you don't see a substantial difference of more than maybe a couple of the percentage points of the 25 percent relative risk reduction observed within REDUCE-IT.

If there is a contribution to biomarker changes, it seems to be relatively small. Amarin did a number of analyses. We gave you a ton of those in your briefing book. FDA also conducted a number of analyses. We cannot definitively say that there was not a mineral effect, but we also do not just see any definitive evidence that there was, and if there was effect, it's quite small.

The point I'd like to hit on really quickly is Dr. Konstam what I think is an understandable struggle, is do you add all these differences together or as separate individual hits, or are they similar? Actually, for that, we have quite a biomarker expert with us today. I'd like to ask Dr. Ridker to come up, especially for consideration about could you add together the CRP and the LDL cholesterol changes.

DR. RIDKER: Thank you. My name is Paul Ridker. I have the honor of serving as a Eugene Braunwald professor of medicine at the Harvard Medical School. With regard to conflicts, I do have a research grant from Amarin to my

institution, the Brigham and Women's Hospital, and I am a consultant for the purposes of this meeting.

The questions that are raised, and that Dr. Konstam and others raised, are terribly important in understanding the development of this drug. My expertise, as many are aware, is nearly 30 years of work trying to understand the relationships of inflammation and heart disease, for better or for worse.

It's my group that was the group that figured out, quite early on, that statin drugs are powerful, lipid-lowering drugs that also lower CRP. And the last time I had the honor of being in front of this committee was in 2008 when we presented the results of our JUPITER trial, which is intimately related to all these issues about statins and inflammation.

I'm going to be quite brief and try to cover all this quickly in four quick points. The first is I actually agree, pretty much, with the FDA's analysis. I think they've done a very thoughtful job of trying to figure out how large is the

worst-case scenario for the potential LDL effect. They came up with 3 percent, and is extremely close to the number that I got independently; and they came up with how large might another effect of CRP be, and they came up with 0.3 percent.

I would say also that it's very important to recognize, as a CRP researcher, this study frankly doesn't have the kind of data you really want to answer the question. When we design our CRP studies, we measure CRP on repeated occasions at baseline and repeated occasions on follow-up in order to get rid of the high variance in that variable.

This is not a biomarker study, so that was not done. So you're being asked to interpret a single value at baseline and a single value at two years. And I'll be honest with you; I just would be very cautious in doing so because that's not how these studies are typically done.

The third issue here really has to do with the core question being asked, is the notion of statin absorption. We have shown that statins

lower both LDL and CRP, but it's one mechanism. It's one drug. It's not two different things going on. So when you use the CTT meta-analysis to figure out what might the worst-case scenario be, it's one drug. It's statin. It's not this plus that. It's a single item. And again, I think that the FDA's analysis on this was really quite thoughtful.

I think also the other thing here that probably ought to be said is that -- and this is complicated, but I think it's worth saying -- as principal investigator of the CANTOS trial, we were able to show that lowering CRP, with a very specific pathway, an interleukin-1 beta inhibitor lowered cardiovascular risk. That's a long way from saying that any mechanism that might raise CRP might or might not have anything to do with increasing risk. We just don't know. We only know that one drug and that one pathway works.

This agent is not related to that, so I don't even know how to answer a question about whether or not the placebo increase would matter.

I've run many trials based on CRP, where placebos go up, placebos are flat, placebos have gone down. There's variation in this.

I guess my last point comes back to the session we just had with the public, frankly, which is to say, yes, I'm a biomarker researcher who's done this kind of work for 25 years, but we do the biomarker work to do the endpoint trial. This is an 8,000-patient, randomized, double-blind, placebo-controlled trial with over a thousand clinical endpoints.

I think, as we heard very eloquently, when I move myself back to practice, it's diet, its exercise, it's smoking cessation, it's a statin. And now, for the first time, we have something else to add to that, and I think at the end of the day, that's what this is really all about. Thank you.

DR. JULIANO: Thank you.

DR. BURMAN: Thank you. Thank you to the sponsor.

DR. JULIANO: Then I had one more series of questions that had come up around the ASCVD risk

score and the various ways we cut that, from a number of panelists. If you'd like, I can address that.

DR. BURMAN: Very quickly.

DR. JULIANO: Okay. The first thing I'd like to say is I'd like to take a step back. Dr. Schatz [ph] is right. We had not provided that data previously to the FDA, nor did we include it in your briefing books. Frankly, we cut that recently in response to the FDA questions and discussion points for this panel because we thought it might be helpful for you in considering how to distinguish these high-risk primary prevention patients.

I think we should start, though. If I can have slide 1 up? And remember, we are also in agreement that this study should be considered as it was designed, and the patient population should be considered as they were specified.

The study was designed to test the primary endpoint in the full=patient cohort, and the primary prevention population was only meant to

represent 30 percent of the patient population. So it was never expected to necessarily achieve statistical significance. Nonetheless, it's been put to this committee and to consider the benefit-risk considerations within that subgroup. But I think it's important to remember, within consideration, that there are some caveats to these types of analyses.

This is the primary endpoint that you saw earlier, where you see a suggestion of reduction within that primary prevention cohort, despite the fact that it doesn't reach statistical significance. We see something similar in the key secondary endpoint. That's slide 4, please.

But then I think importantly -- if I can have the Kaplan-Meir and total event curves of the primary and secondary prevention from Dr. Navar's presentation. While those are getting called up, it's also important to remember that these patients, while it takes a little longer -- slide 1 up, please -- we certainly see benefit early and curve separation early in the secondary prevention

patient population, but it takes a little longer to see it in the primary prevention patient population; particularly in the total events, you see curve separation, and that separation continues over time. So we think that there is benefit here.

So then, how do you consider benefit-risk considerations? If I can have slide 3 up, please? This is the slide that we originally presented. Now, it was brought up whether we could do these risk scores on a continuum, was one of the requests from the panel. We'll say the reason we cut at 10 percent was not arbitrary. The different guidelines either cut at 7 and a half percent to define lower than 7 and a half for the lowest risk, or lower than 10 percent to the lowest risk.

We don't have enough patients below 7 and a half percent in REDUCE-IT, so the lowest cut we can take is 10 percent. And once you get above 10 percent, you're getting to either a moderate or higher risk patient population. So just to note, it wasn't an arbitrary choice; this was sort of to hit with where the guidelines are.

Next, I think there was a question for hazard ratios. Sorry. Can you put slide 3 back up, please?

DR. BURMAN: I'm not sure we have time for that, unless you can just give us the bottom line.

DR. JULIANO: Yes. We were asked for the hazard ratios, so those are also here, presented on this side at the right. And if there are any further questions about how to do benefit-risk, we do think that the new onset adjudicated Afib and the serious bleedings are the appropriate way to look at that.

If the committee has other considerations, we do have Dr. Kowey, who is an expert in Afib and bleeding, and how to consider benefit-risk in these patients. We also have Dr. Busch, who is an endocrinologist, who has a very large lipid clinic and could answer some questions as well about how you translate this to some of your patients.

DR. BURMAN: Thank you both to the FDA and to the sponsor --

DR. JULIANO: Thank you.

DR. BURMAN: -- for those clarifications. We do not have time, unfortunately, to go over the few remaining questions we had for the sponsor. Hopefully, they were answered or we can discuss them for the points of discussion.

The committee will now turn its attention to the task at hand, the careful consideration of the data before the committee, as well as the public comments. I would like to emphasize, and the FDA would like everyone, as much as possible, to give your comments and get your opinions on these questions.

Here is the time schedule. We'll spend 30 minutes on each question, and we won't have a break. But if you need to get food or whatever, just go up and come back. But then around 5:10, if all goes well -- 4:10; sorry about that --

(Laughter.).

Questions to the Committee and Discussion

DR. BURMAN: -- we will be addressing the voting question, and then we'll go around the room, and hopefully we'll end about 5:00 or 5:10.

So we really want everybody's input. Do you have the question, Jay?

Discussion topic 1 is please discuss your interpretation of the efficacy results from the REDUCE-IT trial, including the following: overall strengths and limitations of the data, including the use of a single trial to support a first-in-class cardiovascular outcomes indication and the robustness of the results; confidence in the trial outcomes when considering the mineral oil placebo; magnitude and clinical relevance of the observed treatment effect; and components of the primary composite endpoint or secondary endpoints, including the robustness of the data to support an indication for CV death.

We invite everyone's comments. Dr. Yanoff?

DR. YANOFF: Thank you. I've just been informed that FDA has prepared a response to Dr. Ellenberg's question about competing risks and is prepared to provide that now if there is still concern.

DR. ELLENBERG: I don't think it's necessary

[off mic].

DR. BURMAN: She says it may not be necessary now, but thank you very much. Thank you.

For the discussion question? Yes, Dr. Kraft? Please state your name, of course.

DR. KRAFT: Walter Kraft. I've been struck by a study in which we have dramatic clinical results, but we don't have a very good mechanism of action or biomarker. What I was going to ask the sponsor, but we didn't get time for it, is we have discussed the exposure. The EPA exposure has been linked, in a dose or an exposure response, to a clinical outcome. I think that this provides a convincing mechanistic basis for support.

The only question, again, if we have time for it, I'm not sure if the differences in exposure were a function of proxy for adherence to medications or if there are other covariates that were predicted by exposures that would otherwise assist with restratification.

DR. BURMAN: Other comments? Dr. Wilson?

DR. WILSON: The more I look at the first

forest plot in the Bhatt paper from last year, just about this time, this is an overwhelmingly convincing secondary prevention trial. Dr. Ridker said it extremely well, I thought, is that if you really focus on the secondary, the key where most of the meat is, everything's in the right side of the neutral line, so it's a significant.

The high-risk patients who are at extremely high risk and have secondary prevention, we treat very aggressively with statins. In the modern era -- especially since the pronouncement of the 2018 cholesterol guidelines, but also it was hinted at in the 2013 guidelines -- we reach for the moderate and typically a potent statin, and then we move on from there to assess a second drug.

So some of the concerns go away if we really focus, especially, on the secondary prevention. It's overwhelmingly strong. It's when we get into these other groups, we start having, well, does it work here or does it work there? That's number one.

Number two is not just hazard ratios, in

the modern era, we assess need to harm and especially need the benefit; number needed to treat to benefit and number needed to harm. Dr. Konstam alluded to that. For instance, the 25 percent overall benefit is actually a 4 percent absolute risk versus a 3 percent; 4 minus 3 is 1, divided by 4 is a 25 percent benefit.

DR. KONSTAM: It's the 3 percent [off mic].

DR. WILSON: What?

DR. KONSTAM: It's the 3 percent.

DR. WILSON: The 3 percent is in the treatment arm, so treatment versus placebo arm. The point is the numbers needed to treat look fairly similar to what we've seen for ezetimibe as a second drug, to what we've seen for PCSK9. They're in the 50 to 100 range, especially in the secondary prevention group, and it's convincing. It's when we get outside of that group -- and that's why Ann Marie Navar was trying to make greater sense, I believe, of the primary prevention group, which is diabetics, and making a follow-up analysis to identify the primary prevention, which

are almost all diabetics, and among the diabetics, even those who are at higher risk.

So that's my synthesis up to this point for the number needed to treat and the benefit. As you've heard from my questions, I've still a little bit of a concern is there some number needed to harm, especially for people on multiple oral anticoagulants, that we should be concerned about. I'll stop there.

DR. BURMAN: Thank you. Let me go to Dr. Posner on the phone.

DR. POSNER: Yes. Thank you. I have a couple of patient type questions. A lot of the data is showing in percentages, risks in percentages. The thing as a patient that I would question is, what does this mean in time? In other words, is this going to reduce the time to an adverse effect -- excuse me, increase the time to an adverse effect by days, weeks, months, years, or forever, or it's just going to give me an extra week before something bad happen?

The other question, previous questions, is

what are the effects, particularly on being Hispanic effects, and what outweighs what? So I'm having a difficult time as a patient putting together what benefit I actually get from this when I'm just given percentages of something may happen sometime or other sooner or later?

That's basically my question, is trying to make sense of it, and particularly since there's no mechanism presented for how it works. I think of the old true-true related questions we used to have on boards, on it's true-true, but there's no relationship between the two events.

DR. BURMAN: If I interpret your comments correctly, to make them more of a comment than a question, you're questioning some of the validity of the data, and would like some more information in the future regarding some statistical events.

DR. POSNER: Yes, in numbers rather than percentages.

DR. BURMAN: Yes. Thank you. Dr. de Lemos?

DR. DE LEMOS: James de Lemos. I would echo Dr. Wilson's comment that in the secondary

prevention population, the data are overwhelming and convincing, with a caveat that I'll come back to regarding the mineral oil. They are wholly unconvincing in the primary prevention. We really never got the math, but it's not clear to me that there's even net benefit in the primary prevention cohort.

I do not think we should reward sponsors for enrolling small subsets of primary prevention patients in secondary prevention trials, reporting an interaction that's not significant, and then giving them a broad indication for which we really don't have enough evidence. So it may well be a great primary prevention drug; they just haven't established that yet.

Marv raised a point, and I was not that concerned about the mineral oil until the point was raised, that perhaps the LDL effect is only a marker of broader drug absorption effects. And I don't believe that either the FDA or the sponsor have adequately addressed this. It would have been very simple to do some drug absorption studies,

looking at all of the drugs that patients in this population are taking, including, for example, the antiplatelets and anticoagulants.

One could come up with a hypothesis that it's the delayed absorption of these drugs that leads to less bleeding in the placebo arm rather than more bleeding in the drug arm. So you could come up with a lot of hypotheses. These would have been fairly easy to reassure us about with some simple studies on drug absorption.

With regard to single versus two trials, I'm perfectly fine with a single trial in a secondary prevention population with this level of evidence, but not for a CV death indication, given the p-value that's observed and the issue with mineral oil. I think to get the single trial for a death indication, you've got to have a p-value that's lower than, like was done with the EMPA-REG outcome. But to get that indication, p equals 0.03 is not sufficient.

DR. BURMAN: Just a quick comment to you, a question. You weren't convinced by the OPH session

and the individual who presented the slides of mineral oil absorption versus cellulose?

DR. DE LEMOS: You know, this is outside of my area of expertise, but I guess I'm just -- we focus only on LDL and CRP effects in terms of modeling. Again, I think in the end, I don't believe that it's likely the explanation. In the sponsor's defense, they were unlucky. I mean, they discussed this with the FDA. They picked mineral oil for a good reason, but they got unlucky that it turns out that they may have picked a placebo that's no inert.

But I'm not fully convinced, and I think more could have been done, because this ends up being a big issue with regard to our confidence in the results. In the end, I guess I'd be surprised if it ends up negating more than a proportion of the effect, though.

DR. BURMAN: Thank you. Dr. Yanovski?

DR. YANOVSKI: Thanks. Jack Yanovski. To address the four points, first, I think, again, agreeing with the other speakers, the overall

effect in secondary prevention looks quite strong and convincing, and that one single, very large trial is probably sufficient to support a first-in-class indication for secondary prevention. The robustness of the results are clear from the fact that all components of their composite endpoint were all showing affects in the proper direction.

I think, again, the primary prevention data are a little bit more suspect. I think the mineral oil placebo issue has been adequately addressed by the FDA and the sponsor. I actually think that it's extremely unlikely given the presentation of the FDA that it had a sufficient impact to negate the results that are observed. So I'm going to treat that as an entire class. All of those mineral oil related questions for CRP or effects on other outcomes I think are adequately handled.

The magnitude and clinical relevance of the observed effect is quite substantial. It's enough to move the needle in the right direction for patients who are at risk for cardiovascular

outcomes. So given that we have a lot of potential mechanisms, we don't really know what the particular one that's important. And that's what's led to this, if you will, indecision about what level of triglycerides should it be and what patients should be selected. It's very clear that a secondary prevention has been shown.

The primary prevention issue I think is very suspect, and it may well be necessary to think about the triglyceride level again as a marker of cardiovascular risk. The question of what the right level, 135, 150, or even 200 might be an appropriate cutpoint has not been sufficiently determined and requires additional study, and I think we can recommend that the sponsor do more.

I think in terms of the components of the primary composite endpoint and secondary endpoints, I think except for the CV death, everything else has been pretty well shown to my satisfaction. Thank you.

DR. BURMAN: Thank you. Dr. Brittain?

DR. BRITTAIN: So I don't know how much I

have to add above what everybody else has said. I think I want to talk a little bit about the mineral oil issue. I think I feel that it's probably not a concern, but there is this discomfort that I don't know what analysis to do that completely gets rid of my concern. I don't think there is any analysis to do that will completely allay my concerns.

Although I do wonder, the sponsor mentioned the possibility of regression to the mean because you have to have below 100 to get into the trial, so that could lead to some regression to the mean, and I don't know if there's any experience in other trials that have that LDL cutoff. Probably not, but I just wanted to see if there was any possibility that that could be an explanation.

It seems pretty likely that there is an effect, whether it matters. And again, I think it's not just the worry that it's only the effect on the LDL, but more that it may be a little bit of a canary in the coal mine, that we don't really know what the full effect is. That said, I'm not that worried about it, but it's just sort of a

nagging concern.

DR. BURMAN: Thank you. Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. I think that the data that were presented do show a real signal for efficacy for Vascepa in the REDUCE-IT population in the patients with established cardiovascular disease. I think that the mineral oil issue probably affected the magnitude of that effect. Probably we might have seen more of an effect in the trial than what's real because of this mineral oil possible effect. I thought that the analysis that was done by the FDA, I really appreciated that. What was shown in terms of the LDL effects was really helpful.

I do think that the issue of the second cardiovascular risk cohort, I don't know if you understood my questions. I think that the numbers that you gave me about hazard ratio were not in the correct population. What you gave me was what was in the cardiovascular risk category 2, but not what was shown in slide 92, which was patients without established cardiovascular disease. I think that

that hazard ratio is different. I think it's going to be much smaller.

I completely agree with what's been said, including by Dr. de Lemos and Dr. Yanovski, that this trial really shows benefits in patients with established cardiovascular disease. So I think we have to be careful about that. The magnitude is probably not as much as what was shown because of the concerns. In terms of the components of the primary composite endpoint and secondary endpoints, I don't think that the data are robust enough to support an indication for cardiovascular death.

DR. BURMAN: Thank you. Dr. Konstam?

DR. KONSTAM: Yes. First of all, as far as the single trial is concerned, in and of itself, I'm not concerned about it. If you accept the magnitude of the benefit and the smallness of the p-value, I don't think the issue of replicating trials is that important here.

With regard to the mineral oil, I have to tell you, when I started reading the briefing books, I said, "Why is this even coming to panel?"

And then I read about mineral oil, and I go, "Oh. Okay. That will be a really interesting discussion," and has been. I agree with others that I don't think we can be completely clear. I'm very impressed with the number of analyses that were done, very cogent analyses. I can't think of how you could do better on both the sponsor side and the FDA side.

At the end of the day, I think we're going to have to say this is an overwhelming effect. It's probably not the mineral oil, and probably just accept that. I don't know any other way, other than having to do a whole other trial, which I'm not sure I would recommend.

With regard to the issue that Dr. Wilson brought up, and also Dr. de Lemos, about the primary versus secondary prevention, my first reaction, as it always is, is, hey, look; let's look at the trial as a whole. Let's look at the one question being asked in the entirety of the population, and let's say that's the thing we know, that this population generated the probability of

benefit that we saw.

That's the thing we know for sure;' right? And then you start getting into subgroups, and my feeling about subgroups, I'm sure as others agree, is they're fun to look at, they're interesting, they drive other interesting studies, but just consider them that, and go back to what the entire study says.

In this case, the thing, unfortunately, that really gets me, when I look at this above and below 10 percent thing that the sponsor did, I'm startled by the fact that below 10 percent, it becomes a qualitative subgroup difference. By the way, this is a post hoc subgroup of a subgroup, so be careful. But just taking it as it is, I would say look at the entirety. The entirety is probably the higher the risk of the patient, the greater benefit you get. Overall, there's going to be a benefit. As you go down in risk, you're going to see less benefit, but that should be driven by a reduction in the event rates. It shouldn't be driven by a shift to the negative. It should be a declining

risk difference.

So the analysis that the sponsor did, despite I shouldn't really believe it, it's kind of startling that they've identified a subgroup of a subgroup that actually goes in the wrong direction. That to me sort of shifts me to say I'm just queasy about the primary prevention population. I'm still not quite sure about it, but I'm very sure about the secondary prevention one.

DR. BURMAN: Thank you. Dr. Newman?

DR. NEWMAN: Connie Newman. First of all, I'm going to speak about the mineral oil as placebo, but I first wanted to thank the sponsor for running this large cardiovascular outcomes trials for 4.9 years as a median, because I've done several trials, and I really know how much effort it takes to do this, and I am a member of the cholesterol treatment trial, its collaboration.

So concerning the mineral oil, I want to add that we all, many of us, ingest mineral oil because it is in food. It's used sometimes to shine apples. It's used sometimes in baked goods and

packaging. But the amount that we usually take is about 30 or 40 milligrams a day, and the patients in the placebo arm ingested 100 times that amount for about 5 years.

There has been concern in the food industry about the limits of mineral oil that should be allowed in food, so there have been studies, autopsy studies, showing that mineral oil hydrocarbons are present as microgranulomas and sometimes granulomas in the liver, in the lung, in the spleen and adipose tissues, little of some amount in the heart, and many organs.

Those are microgranulomas just in people who consume the normal amount of mineral oil, which is much less than what the patients took. There also are studies in people who are alive, biopsies of adipose tissue showing mineral oil, hydrocarbons, and microgranulosis.

So that gives me pause when I think about this study. I was waiting a long time for this study to complete, and it makes me question whether this mineral oil placebo is more harmful than we

know, than we have thought about, or is there a benefit of the icosapent ethyl? I don't really know the answer. I'd like to believe that there is a benefit of the icosapent ethyl, but it's of a lower magnitude than we have been talking about.

Also, I think there should be some studies in the patients on placebo to look at mineral oil in their adipose tissue. I just wanted to add that to the conversation.

DR. BURMAN: Thank you. Dr. Ellenberg?

DR. ELLENBERG: I want to agree with what Dr. Konstam said in the first part of his comments about this is a single study, it has multiple subgroups, and I'm inclined to give the biggest part of attention to the overall results. As Richard Peto always said, "The best estimate of the effect in anybody is the overall results," and not when you start slicing and dicing.

For that reason, there are certainly some uncertainties here and there in these data, and most of them relate to, I think, the primary prevention cohort. But it is not surprising that

in a somewhat smaller cohort -- which is not tiny. It's still a substantial number of people, and it certainly went in the same direction. I think if you did some kind of simulation, you would find that it was not at all unusual. If the overall result was similar in the groups, that you would find this kind of difference.

Even with the above or below 10 percent, as you said, it's sort of a post hoc, it's cut, and my feeling is I might tend to leave it to judgment, clinical judgment, about who should get it. But if I had to bet, I would certainly bet that it has some effect in the primary prevention population, and I'm not going to give very much credence to the post hoc cutoffs.

DR. BURMAN: Thank you. We only have 4 minutes. Dr. Meininger?

DR. MEININGER: Yes. I want to actually add on to Dr. Ellenberg's and Dr. Konstam's thoughts there. It's a large study. There are lots of subgroups, and we can break it down. If you actually look at the total number of subjects in

that one group with the less than 10 percent with diabetes, it calculates about 5 percent of the entire study, and, again, looking at subgroups of subgroups is a bit of a challenge.

I'm also, besides struck by the overall results, and, obviously, other learned bodies and associations have already come out with recommendations for use in a rather broad population, again, given the landmark results of this. Could you cut the data in smaller pieces? Of course, you can.

Obviously, that's something I think that the sponsor and the agency can discuss in final review. I think it's very difficult, again, to take a look at specific subgroups and try to make more or less of it. I think it's the totality of the data that should be looked at.

DR. BURMAN: Thank you. Last comment, Ms. McCollister-Slipp?

MS. McCOLLISTER-SLIPP: I just wanted to speak broadly about the need. I know there are a lot of cardiologists and endocrinologists on here,

but I'm speaking as somebody who takes a statin, and aspirin, concentrated EPA prophylactically. My cholesterol is perfect, my triglycerides are perfect, but I still stick with it because I need prevention. I've got lots of complications from diabetes.

My mother has an adverse event to statin; it's pretty significant. But she keeps getting stuck on it and put back on different versions of statins because people have been committed to the notion that statins solve every problem on the planet, it seems, and she's experienced several adverse events.

Given the significant adverse events that you see with statins and the significant need for a cardiovascular risk reduction, and maybe not slam-dunk data, but pretty good data about potential benefit, my inclination is to let something go onto the market that does have demonstrated benefit for which the data may not be perfect, but certainly can be compelling, and then let's see what happens in the clinical setting.

Given the safety profile of other medications that we've looked up, this one looks pretty good to me, especially compared against the relative risks that patients are trying to mitigate with our physicians.

I think the point that was made previously by the patient that spoke, and I believe one other person, indications matter in terms of access. It's an issue that I've experienced on a number of my medications, where the sponsor did not have an indication, and I used it off label. That's a real clinical issue, and what we decide and how the agency decides to approve a medication has real implications on what patients have access to and what tools are available to them and their physicians. So I think we need to think about the full ramifications of how we vote.

DR. BURMAN: Thank you all very much.

In summary to question 1, this is my interpretation. Please let me know if you have any questions or comments that we could put into the record. There seemed to be a consensus that the

benefit in the high-risk patients was very clear. The benefit in the secondary prevention is very clear. The benefit for primary prevention is a little less clear and maybe needs further studies.

The mineral oil issue and whether it adversely affected the outcome of the study or the findings in this study is somewhat controversial. Some people thought it might and some people thought it might not. There is a question about the long-term effect of mineral oil in and of itself. I think we agree that the higher the risk, the greater the benefit; the lower the risk-benefit, the benefit is less and may be less clear. Then, we seemed to all agree that an indication for cardiovascular deaths doesn't seem justified.

Anybody have any comments? Yes?

DR. NASON: Just to add one thing, I agree with everything that's been said, which is why I --

DR. BURMAN: Would you state your name, please?

DR. NASON: Sorry. I always forget that part. Martha Nason.

DR. BURMAN: Thank you.

DR. NASON: I agree with everything that's been said. I just want to add one little comment on the mineral oil because I have been feeling very unsettled about it, and I still do, but I started trying to do my own -- I'm a statistician, which I said at the beginning. I started trying to do my own little calculations about what if we take the people who are in the retrieved dropout cohort who dropped off of mineral oil, dropped off of placebo, and use them as sort of one estimate of what might happen if you didn't take the mineral oil anymore.

There are all sorts of problems with this analysis, and the stuff the FDA did, of course, is much more thorough, and much more careful, and has real data, not just scribblings. But even then, I was still doing my little back of the envelope. I was still getting p-values like 0.0008 for the little cases I was making up.

So that actually made me feel a little bit

better, so I just thought I'd throw it out there in case it made anyone else feel better that, yes, even if we allow that there was a mineral oil effect of a couple percent, is sort of what it came out to with those assumptions I was making, we're still finding a pretty significant effect.

DR. BURMAN: Appreciate that very much.

Question number 2 for discussion is please discuss your level of concern about the new safety findings of increased risk of atrial fibrillation, atrial flutter, and bleeding events from the REDUCE-IT trial and whether labeling can reasonably manage these risks. I would also like to cordially invite anyone who hasn't spoken yet or has strong feelings to make your comments. We would like full participation.

Dr. Konstam?

DR. KONSTAM: Yes, just my thoughts. I'm not very concerned about the Afib issue. I don't think it has any major impact on the long-term effects in the population, and I can live with that. I'm uneasy about the bleeding, and I don't

1 think I'm so uneasy that it kind of moves the risk
2 ratio to the other side, but I would consider how
3 do you mitigate that, how does the labeling read,
4 and should there be a warning about that.
5 There should be some mitigation plan. I
6 think the bleeding issue is real, and I don't think
7 we know, really, how it's impacted. It could be
8 significantly impacted by other antithrombotic
9 agents, and I think there should be a way to try to
10 mitigate that.
11 DR. BURMAN: Thank you. I would make the
12 comment that I was impressed that there wasn't
13 major bleeding events with bleeding. And maybe it
14 could be controlled, but it is recognized, but
15 still is a perfect issue to bring up. Everyone has
16 their opinion on the data.
17 Dr. Ortel?
18 DR. ORTEL: Concerning the bleeding events,
19 yes. There are a couple of points that I thought
20 could be looked at or could be considered. And I'm
21 speaking at it as usually when somebody says it can
22 be addressed in clinical practice, the way it gets

1 addressed in clinical practice is when the patient
2 has bruising, they get referred to hematology, and
3 that's considered the answer.
4 Some things that might be valuable to look
5 at would be whether or not the patients who had
6 major bleeding events also had minor bleeding
7 complications: bruising and other things that
8 might identify patients that you need to think
9 about; stopping a drug or reconsidering the drug.
10 Another thing to think about is during the
11 course of this study, patients were having surgical
12 events and procedures, and was there any mitigation
13 plan? Was there anything for how perioperatively
14 these drugs were managed and whether or not that
15 led to any type of problem?
16 The other thing to stop and think about is
17 when we're talking about patients and bleeding
18 events, really, I'm not going to give them anything
19 to make them more hemostatic. It's going to be
20 coming down to deciding what might you pull away to
21 decrease the bleeding complications that the
22 patient has, because most of the things I give to

thrombose, or give to hemostase, can cause thrombotic events.

So it does come down to thinking about what might go into a label, how would you evaluate this, and what would you do without going down a very long slippery slope.

DR. BURMAN: Thank you very much. Dr. Posner on the phone.

DR. POSNER: Yes, thank you. I'd like to echo those comments about bleeding. As someone who had atrial fibrillation and is on a NOAC, and extremely concerned as an individual about stroke and bleeds -- when I had to make an informed decision about what NOAC I went on or didn't go on, because those rules have changed over the last 20 years almost on an annual basis, I think it's critical for the labeling and decision information about what the benefits are and what the risks are as far as the bleeding goes

It's more than the small print in the labeling, but it has to be something that the doctor prescribing it is going to be able to

explain in words of one syllable or less to the patient who has to make a decision if they're going to take it or not, because bleeding and atrial fib patients, particularly the elderly ones who are worried about stroke are frightened and may not be able to make an informed decision if it's not explained to them correctly. Thank you.

DR. BURMAN: Thank you. Let me just ask very quickly, for those of you who've spoken about the bleeding, do you think it ought to be a black box warning? Should it be just patient and doctor education? Should it be just in the package insert? Dr. Konstam?

DR. KONSTAM: I'd leave that to the FDA to think about when they give black box warnings or not. I personally wouldn't come down at this moment one way or the other, but maybe I'm just chickening out.

DR. BURMAN: Thank you. Dr. Kraft?

DR. KRAFT: Dr. Kraft. There have been some questions about number needed to treat and number needed to harm, and I think I just want to remind

that the number needed to treat, the endpoint at the end of it is a composite endpoint. The number needed to harm I think qualitatively is much less of concern. If we think about Afib or bleeding, not a particularly strong hemorrhagic stroke signal. So I think that we can't just use a number needed to treat versus number needed to harm and compare these as if they're equal.

The other piece that I would say is we've been talking particularly around the indication for primary prevention, at which safety becomes much more important because efficacy, the rates are much lower. So when we think about the relative safety, we have an approved drug for which we have a fair amount of safety information, and better yet, we have a mechanism in the modern era, real-world data, or postmarketing mechanisms by which we can ascertain using large databases, Sentinel or whatever the other tools that we have at this point.

So I think that probably when I think of the less benefit for primary prevention, I want to put

on the other side of the ledger the less risk in terms of the safety and the other tools we have in the modern era to essentially re-look at this issue years down the road and months down the road.

DR. BURMAN: Thank you. Dr. Chrischilles?

DR. CHRISCHILLES: You said you wanted to hear from all of us, so though I don't have a lot more to offer, I would agree that I'm not concerned by the magnitude of the two safety considerations, atrial fibrillation and bleeding, in that I think that they can be effectively handled through labeling.

We do this all the time, and they seem to be concentrating in people who already have experience with these types of events, people who are on antithrombotics or monitoring for bleeding events; people with a history of atrial fibrillation who are familiar with its presentation.

So I think labeling is probably the appropriate solution. I would also echo that I think that we do have good opportunities in the postmarketing surveillance arena to be able to

monitor from both of those events, especially the serious bleeding, where I think there's a fairly reassuring bit of information from the trial that we could still monitor for the occurrence in the real world with our existing surveillance system.

DR. BURMAN: Thank you. We definitely appreciate your input. We'll come back. Let's go to Dr. Wilson.

DR. WILSON: I agree. Some sort of postmarketing surveillance project would be very helpful to really have a better sounding, so to speak, of how much of an issue this is. One of them that comes for patients on anticoagulants is when they initiate high doses of an IPE drug, whether it changes their INR. I'm not sure I've seen that information. That would be very easy to obtain.

Another one is I don't have any feeling for persons on more than one antiplatelet therapy and whether the dose of aspirin makes a difference. For instance, there is some real expertise in this room about clopidogrel and a dose of aspirin and

bleeding, so does that issue hold in the case of a high-dose Omega-3 EPA drug as well?

DR. BURMAN: Dr. Nason?

DR. NASON: Martha Nason. This is actually more of a question to the clinicians, because I'm surprised to hear people say they're not worried about the Afib. Just again, without a clinical background. I looked at the, admittedly, subset of people who did have the Afib history, and you're talking about their estimates are 12 and a half percent in those treated, among those who had Afib history versus 6 percent among those who didn't.

To me, even though the numbers are small, it's about 3 to 400 per arm, that seems like a -- it's a hazard issue of 2. It's statistically significant. It seems, to me, like a place you wouldn't want to prescribe this.

This is actually just, really, a question to my clinical colleagues of are you not worried about that because this is 24-hour hospitalization or hospitalization for at least 24 hours, because that seems like a manageable risk, or because this is a

subgroup? I just would like to hear more because, to me, that looks like a flag that I would pay attention to.

DR. DE LEMOS: James de Lemos. I'll just answer. It's balanced against a reduction in cardiovascular death, so it's meaningful. I think it is a clinically meaningful outcome, and even minor bleeding is a clinically meaningful outcome, but we're balancing it against a dominant outcome that's statistically significant. That's the way I would interpret that.

DR. NASON: [Inaudible - off mic]?

DR. DE LEMOS: Yes, whether you would choose to give this to somebody with Afib, some individuals may choose not to, but we don't know that they don't drive the other benefits in that population. They're also at high risk for myocardial infarction, and stroke, and cardiovascular death, and they may well benefit.

DR. NASON: Thank you.

DR. BURMAN: That was Dr. de Lemos. Thank you.

Dr. Konstam?

DR. KONSTAM: No. I just wanted to come back to a thought that Dr. Wilson raised when he first opened the discussion, and other people have commented on the relationship between risk and benefit. Looking at the primary prevention population, assuming that we wind up recommending approval of that entire population, I would at least want to think about working into the labeling the issue of risk-benefit as you go to lower risk populations, and you're not lowering the risk of bleeding.

So when clinicians are thinking about this, I think they should be thinking that as you go to that low-risk population, the risk may be catching up to the benefit.

DR. BURMAN: Thank you. Anybody else have any other comments? We really welcome all comments on this issue, even if they're repetitious, because it tells what the committee feels.

(No response.)

DR. BURMAN: Well, my view is that the risk

for atrial fibrillation and atrial flutter, it seems to be higher, but the mechanism is not clear, and I'm not sure it's related to this study itself. The bleeding seems to be higher as well, but as was pointed out in the briefing, the risk for major bleeding events wasn't that much higher and wasn't statistically significant.

So I think the comments that were made by Dr. Ortel are very telling and appropriate regarding other findings that are clinical that may increase the risk of bleeding.

Anybody have any other comments?

(No response.)

DR. BURMAN: Then, what I'd like to do is summarize this question, and again, I want your comments and opinion. I think there's consensus that there was a risk of atrial fibrillation and flutter. It may be related to the study or it may be serendipitous. But on the other hand, it's something that can be monitored and treated. I would note as well that the risk of atrial fib and atrial flutter seem higher in people who've had it

previously.

The question about bleeding is more controversial. Even minor bleeding may be relevant, and further studies probably should be done to investigate that. We don't have any information, as Dr. Ortel pointed out, regarding bleeding, survival or bleeding episodes during surgical events or other aspects that may increase the likelihood of bleeding home; all good points. People think there should be a postmarketing study regarding surveillance and bleeding, and probably atrial fibrillation and atrial flutter as well.

Anybody have any additions or comments? Yes, please? State you name.

DR. ORTEL: Tom Ortel. I think that the postmarketing surveillance also should -- potentially, if you wanted to focus on a group of people, it would be the anticoagulant population and the other antithrombotic population just to see. I was struck by just this small number of people who were on direct oral anticoagulants. The very limited data that we have

in that subgroup should be looked at postmarking surveillance.

DR. BURMAN: Thank you very much.

Dr. Yanovski, you had a comment?

DR. YANOVSKI: Jack Yanovski. Just to make sure that we also included in the summary that we think that most of these, if not all, can be reasonably managed the labeling.

DR. BURMAN: Thank you all. Good. We're moving along pretty expeditiously, so we'll take this next question, and probably we'll then, if there's time, take a 10 to 15-minute break before we go to question 4.

With regard to this discussion question, the applicant has proposed an indication for cardiovascular risk reduction in adult patients with triglyceride levels greater than or equal to 135 milligrams per deciliter and additional risk factors for cardiovascular disease without regard for age, diabetes status, or adequacy of low density lipoprotein control.

Please discuss the population beyond the

subset of patients with established CVD for whom you believe the data from REDUCE-IT provide evidence of cardiovascular risk-benefit, addressing the following factors to include, but not solely: age; diagnosis of diabetes; additional risk factors for cardiovascular disease; plasma LDL concentration; plasma triglyceride concentration; intensity of statin therapy; or any other factor you think is important.

Again, I would like everybody's opinion. The floor is open. Dr. Nason --

DR. NASON: I just have a --

DR. BURMAN: -- please put your name.

DR. NASON: -- sorry. Martha Nason, just a quick question. This doesn't say anything about statins. Is the proposal, then, not for people who are already -- it's says "statins" down below, but as far as the proposal, this trial was in people -- or at least the primary was -- who are on statins. Is the proposal on statins or they don't have to be on statins?

DR. BURMAN: Does the FDA --

DR. SHARRETTS: [Inaudible - off mic].

DR. BURMAN: I think they're on statins, unless the FDA disagrees.

DR. SHARRETTS: Are you asking what was in the applicant's proposed indication?

DR. NASON: Yes.

DR. SHARRETTS: Yes. Okay. In the proposed indication it was to reduce the risk of cardiovascular death, MI, stroke, revascularization, and unstable angina as an adjunct to statin in adult patients, blah, blah, blah; yes.

DR. BURMAN: Thank you. Dr. Weber.

DR. WEBER: Yes. I think this has been brought up before in the discussion on question 1 about primary prevention, and I guess I have some concerns in terms of looking at that. The proposals for triglyceride 135 are higher in one risk factor, and I think the FDA's analysis showed that in the group 2 analysis, there were at least two risk factors; so a very high-risk population. So that gives me pause.

The other issue, obviously, we've been talking a bit about the mineral oil, the elephant in the room, and if there's uncertainty about that as it relates to the effect, and the fact that, actually, despite the trend being there, I didn't see statistically significant effects on the primary outcome with the secondary group, and I think that's enough to say yes for secondary prevention, but primary prevention, no.

DR. BURMAN: But maybe you could expand on that a little bit, discussing some of the specific factors there; what you think the age should be.

DR. WEBER: Well, again, I think it's premature. I'm actually putting a wet towel over all of it and not talking about specific factors. I don't think we're quite there in regards to primary prevention.

DR. BURMAN: Dr. Kraft?

DR. KRAFT: I think we're stuck with risk factors, particularly triglycerides, as a not ideal biomarker, and that the risk scores potentially would be helpful. But I do want to circle back to

the EPA exposure, and I would just maybe ask the FDA to reconsider the stringency for which this was not considered as a viable biomarker.

This would be used as a biomarker to identify subsets that had exposure that would lend itself to better outcomes. And if only because there seemed to be an exposure-response, if the assay was not reliable, you would expect there to be regression in the mean and no actual exposure-response; we saw on exposure-response.

So I would just invite the FDA to really consider to look back at that. You could probably do stability, short stability testing, and see if you could bring that data in to modify risk score and a exposure-response relationship.

DR. BURMAN: Thank you. Dr. Posner on the phone?

DR. POSNER: Yes, I have to agree with the previous comments about primary in that I don't think it would be worthwhile. Secondary, the thing that I'm troubled by is adherence. People that are following an incident or an event may be on an

anticoagulant, will be on a statin, will be on an ACE inhibitor, will be on a platelet medication. By the time you're finished taking all of the meds, you're not going to have time for food.

The problem with this is, since we still do not have a mechanism, we don't know what the additive value of this particular medication would be with the statins, the ACE inhibitors, the beta blockers, and the NOACs. So I agree. For primary, I don't see a purpose for it in, and the secondary, I think there should be a little bit of caution as to whether you're going to do this.

I know for marketing, they'd love to sell it to everybody. It seems they're [indiscernible], as they did with the statins. But I think we have to take into account the patients and what they're willing to take, or what the statistical benefit actually is. Thank you.

DR. BURMAN: Thank you. Dr. Brittain?

DR. BRITTAIN: I think the indication needs to match the study. I am comfortable including the primary prevention group. The fact that it wasn't

significant wasn't, in a sense, not fair because it wasn't powered for that. But at the same time, that group, if I'm remembering correctly, had to have diabetes, and I don't remember if it was another risk factor besides diabetes, and the proposed indication does not seem to reflect that.

DR. BURMAN: Thank you. Dr. de Lemos?

DR. DE LEMOS: I'd strongly agree with Dr. Weber's point that the drug should be approved for secondary prevention only, and there should be no subsets for primary prevention. This is a game, and we're getting played, basically. These are not subgroups; these are different populations. We don't treat patients with coronary disease with the same set of drugs we treat patients within primary prevention.

What they've done is asked us to consider this as a subgroup of an overall trial rather than demonstrating favorable risk and benefit. We asked the sponsor to provide us with numbers, how many events were prevented, how many safety events were prevented. We never saw that. There are 17 total

event differences in the CV cohort 2, and based on what Dr. Low Wang says, that probably even exaggerates the difference in true primary prevention. And that's going to be balanced, as Dr. Kraft says, by some excess in Afib and some excess in bleeding.

If we allow a primary prevention indication for this drug now, it will never be studied in primary prevention, and we'll never know. It may be a great drug for primary prevention. I'd hope it will be, and it should be studied, and it should be studied against a non-mineral oil placebo, and we should find out just like we did with statins; demonstrate efficacy and safety in secondary prevention, and then move on and demonstrate, in a completely different population, independent efficacy and safety, so that we know what primary care physicians should be doing.

DR. BURMAN: Thank you. Dr. Wilson is next, but I would like to mention as well the question asked for all these subcategories, what you think regarding approval for age, diagnosis, and LDL

concentrations. So maybe some of you can comment on that as well.

DR. WILSON: I'll try. The first thing that strikes me is -- I'll go to the dose of intensity of statin therapy. I would think moderate to high risk diabetic patients, the first thing we would do is to make sure they're on a moderate to high intensity or maximally tolerated statin as the next step, before a second drug. That addresses issues in this trial because we have a whole range of statin doses that were used in addition to the EPA drug. So that's number one, the statin dose, I think personally, and that would go with most of us as lipidologists do for care of patients.

Dr. Ann Marie Navar, Ann Marie is to be complimented for her analysis. I voice some concern about taking each of the risk factors and using a score while a person's already on a statin. One of the first things is I think they could undertake a sensitivity analysis, but I also think we're likely to be changing over the years our cutoffs for risk scores and/or algorithms, for risk

scores will change. I've seen that over the years myself from personal experience.

I would also encourage, in her follow-up analyses, since we're first seeing this, to see if that could be simplified. One of the simplest things is to count the risk factors. Could you do that and not get into this 10 percent score, the number of risk factors, for instance, diabetes, others, and her analysis would be simply another way to move forward to make this practical, because four or five years from now, I don't think people are going to necessarily go back to the current risk algorithm and try to estimate the risk; and they're going to say what do I do as we transition and go forward? So counting the number of risk factors in a primary prevention.

You can guess; I've already said this. I'm in the James de Lemos camp. That may be a way to develop a new study, especially, to identify the high-risk primary prevention group. It might even be a project going forward, and some of her analyses could help guide how that would be

designed.

DR. BURMAN: Thank you. Dr. Ellenberg?

DR. ELLENBERG: I think the consistency across the different levels of all these categories is quite amazing. It's very, very consistent. I don't see that there's any basis to say there needs to be some limitation, at least within the limits looked at in the study. I don't know about going beyond who was studied, but certainly within the study, the results are very consistent. So I wouldn't see any basis for making any other kind of limitations.

DR. BURMAN: Thank you. Dr. Meininger?

DR. MEININGER: Hi. Gary Meininger. I think going back to what Dr. Ellenberg and Dr. Konstam had said before, and I also commented on, again, the best way to look at this trial is the totality of the data. To sort of cherry-pick one subgroup versus another is difficult.

I think as it relates to labeling, obviously, that's something that the FDA does very well. I think in terms of how to label this, I

1 think obviously the description of the study should
2 be provided in detail in Section 14, obviously,
3 describing the types of patient populations that
4 was enrolled.
5 I think from an indication perspective,
6 again, I think sometimes simpler is better, and I
7 think the FDA has prerogative about exactly how to
8 label. I think if you start labeling for each
9 individual risk factor, it's going to get very
10 confusing, and prescribers may not ultimately
11 prescribe for this. So maybe secondary prevention,
12 established disease, and at high risk, then
13 prescribers can look back at Section 14 to see if
14 their patient fits those high-risk factors.
15 DR. BURMAN: Thank you. Dr. Konstam?
16 DR. KONSTAM: As I keep listening to the
17 discussion, I have enormous respect for a lot of
18 the very smart comments that were made,
19 particularly Dr. de Lemos' comment that, hey, this
20 isn't a subgroup; it really is two different
21 populations that have been stuck together.
22 Nevertheless, they tend to be moving toward the

Ellenberg school.

So here's my thought. My inclination is toward approving the entire population, but I would put a big asterisk next to that because I would like to see the FDA go back and do more work on this, and specifically really look at net clinical benefit a few very hard ways, and look at it specifically in the primary prevention versus secondary prevention, and what is net clinical benefit with regard to the adverse effects for patients who have a magnitude of effect that looks like the primary population before I would come down and finalize.

I think if that really splits out, I might say, no, let's stick to the population. It seems more secure. And I would, as I said, deal with it in the labeling. I would identify that the net clinical benefit may be greater in patients who have more advanced disease.

I'll point out I agree they're not the same population. I agree that it would be nice to do more studies in primary prevention. It's really

hard to believe that the mechanism of action that is going on in patients with established disease is going to be different in the population that's probably got a call to establish the disease because of the nature of their risk factor, or soon to get it.

I think that the comments have been made that prevention takes longer to see, and it could be that it really requires a longer timeline to see the benefit in the prevention. That's what you would expect, so that doesn't fully surprise me. That's the way I'm going.

DR. BURMAN: Thank you. We have five more people who want to speak, and we have about 10 minutes? Dr. Newman?

DR. NEWMAN: Connie Newman. I think the indication should be for patients who are on maximally tolerated statin therapy and have either atherosclerotic cardiovascular disease or diabetes. Patients with diabetes have a high risk of cardiovascular disease, and I'm wondering whether we should just have the indication for all patients

with diabetes who have hypertriglyceridemia.

The question I have is hypertriglyceridemia to me is a triglyceride over 150. I'm not sure -- I would prefer the indication to remain that way and not to have to say over 200, even though that is what was studied, but I think that's up to the FDA. And I don't believe there should be an upper age limit. The indication should be for adults.

DR. BURMAN: Meaning over 21 or over 18?

DR. ELLENBERG: I'm trying to figure out whether it should be for adults 40 years of age and older, but there could be exceptions to that. So I'm not sure how I would word that.

DR. BURMAN: Yes, it's a hard question. Dr. Yanovski?

DR. YANOVSKI: Jack Yanovski. I think for all of these questions that are being asked for topic 3, we have to go back to the trial design. It was limited to men and women greater than or equal to 45 years of age with a history of CVD, and men and women who are greater than 50 with diabetes

requiring medicine and at least another CVD risk factor.

Those are the minimal requirements that would have to be present for an approval because that's what was studied. Again, if someone had cardiovascular disease and were 44 years old, I don't think I would have a problem treating that person. But I think we don't have any clear evidence that the 20 years between age 20 and 40 of treatment would necessarily lead to benefit rather than cost and risk for other complications that, again, we don't know enough about.

So I think to refer back to the protocol design would limit us in terms of age, and diagnosis of diabetes would be required unless there is CVD. The additional risk factor has to be at least 1. The plasma LDL concentration needs to have been controlled. According to the protocol design for 100, the TG, I understand it was allowed to be down to 135, but that was really in order to make sure that they didn't drop anybody out. The goal was 150 and above, so that should certainly be

a requirement.

The intensity of statin therapy, it looks pretty clear that statins are a requirement for most of the patients who would be considered for this, so probably the requirement. I think that's all. Thanks.

DR. BURMAN: Thank you. Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. I would say one of the things that we did learn from this study that hasn't been discussed yet is just that it did a very, very good job of distinguishing patients with diabetes at high risk and low risk. All of the patients in that risk category 2 had diabetes, but it shows that not all patients with diabetes have the same cardiovascular risk.

So I think that the study strongly supports approval for this drug in patients with known ASCVD. I agree with what's already been said by Dr. Weber, and Dr. de Lemos, and Dr. Wilson, and others, about the fact that I don't think that this study supports its use in that second category; so patients without established ASCVD.

1 But just looking at the way this question is
2 worded, I think we have to look at who was studied
3 in the population in REDUCE-IT and qualify patients
4 with established CVD, the age cutoff of 45 and
5 above, with or without the diagnosis of diabetes,
6 and then on maximally tolerated statins.
7 DR. BURMAN: Thank you. Dr. Brittain?
8 DR. BRITTAIN: I have a question for the
9 FDA. I want to understand why this study was
10 designed with the 70 percent secondary, 30 percent
11 primary. I didn't know if that was something you
12 wanted or something the sponsor wanted. What is
13 the philosophy behind that? They weren't
14 powered -- there was no power done within the
15 cohort, so what was the role of the different
16 cohorts and stipulating those percentages?
17 DR. SHARRETTS: John Sharretts. I will
18 answer part of the question, but then I think I'm
19 going to kick it back to the sponsor. As the
20 sponsor mentioned, the trial was conducted under a
21 special protocol agreement, which means that it's a
22 formal arrangement for the FDA and the sponsor to

hammer out the major components of the trial.

Now, this was done probably between 2010 and 2011. I'm not sure where the idea of the second cohort came. We could review minutes on that, but I suspect that the FDA suggested that they needed to get a certain number of patients to get that indication, but I believe that we did agree, depending on review of the data, that it might be possible to get an indication for the second subgroup with the trial design.

I'm not sure the details of how the design came. Typically, with a special protocol arrangement, the sponsor submits a protocol, the FDA gives comment, and then we agree on the terms. But I think I'll let the sponsor talk about some of the details of this early meeting.

DR. BURMAN: Thank you. It isn't relevant to the question and, of course, it's an important issue, but it doesn't relate directly to this question. So if the sponsor wanted to respond, and I mean really quickly about this, that would be fine.

DR. JULIANO: Thanks for the opportunity to clarify. We agree, a special protocol assessment means the critical components of the SPA are agreed to in design, and it was agreed that this 70/30 split would provide a sufficient representation of both primary and secondary prevention to understand if there might be similar benefits.

It was never designed to see statistical significance, frankly, in either of the subgroups. There just were more events in the secondary prevention group, and we were able to achieve it with a large relative risk reduction. But it was designed to basically ask are you seeing, essentially, a similar magnitude of benefit, and the statistics would suggest we are.

Just really quick, the rebending that you had asked for on the 10 percent above and below, or the 10 percent above or below ASCVD risk score, that was the rebend CV risk, too. So all of the primary prevention patients that had history of cardiovascular disease were pulled out of those. So I do believe that was what was asked for

earlier, just to clarify.

DR. BURMAN: Thank you for your succinct commments.

DR. JULIANO: Thank you.

DR. BURMAN: Dr. Yanoff, you had a comment?

DR. YANOFF: I'm not going to be able to comment on the rationale for the design, but I didn't know if this comment might help you a little bit, thinking to some of the diabetes meetings you may have attended. This is a very common approach for these types of trials, where you want to enrich for events, so you may design a trial to have the larger group be the secondary prevention because you expect more events in those, but you also want to see if the effect is similar in a lower risk group. But it's not a requirement to have statistical significance in both groups of patients, and we look at the trends.

I think there is no guarantee up front whether the results would support the entire population, or a subset of the population. It really depends on the outcome and the robustness,

but there's no expectation up front, that for every patient type that the drug is indicated for, that you're going to see statistical significance in the outcomes.

DR. BURMAN: Thank you. Let's return back to this discussion point. Dr. Wilson, you had the last comment.

DR. WILSON: I think Dr. Yanovski brought up a really important issue, is are we asked to address this, especially from the perspective of what was in the REDUCE-IT trial and the population of -- these are middle-aged to older diabetics, and we have a tremendous number of diabetic patients at risk, but we really don't have information, numbers. Dr. Low Wang, I think, brought up 45 or 50. I would be very concerned about trying to extend these sorts of findings for an approval for the very young. The FDA needs to consider this very seriously.

The other one, just to mention, those of us as endocrinologists, these need to be based on outpatient triglycerides for patients not recently

hospitalized because things like diabetic ketoacidosis can really shoot up triglycerides, and you'll get a false impression of, really, the long-term triglyceride exposure to the patients.

DR. BURMAN: Last comment, Dr. de Lemos?

DR. DE LEMOS: James de Lemos for Dr. Yanovski. This strategy, though, of allowing a broad indication for relatively modest size subgroups that are fundamentally different seems risky, I guess particularly when these drugs are on the market for other indications, like the diabetes drugs. We did not give -- for the diabetes drugs, for the cardiovascular indications, they were labeled in the beginning fairly narrowly to the secondary prevention populations, even though there were a handful of primary prevention individuals enrolled; partly because there looked to be qualitative differences, but partly because those subgroups are small.

The point I would just make is that this drug is on the market for diabetics with high triglycerides. You can use it. It's FDA approved.

It's just a question of can you say that it improves cardiovascular outcomes in that group? And I think that bar should be really high because, then, we're giving the blessing that that's a true finding, that for primary prevention in diabetes, this drug has a favorable effect on cardiovascular outcome.

DR. YANOFF: I would agree with everything you're saying, and I was specifically just simply trying to address the question of why it was designed that way, only 30 percent. I just think it wasn't necessarily a requirement or sufficient to label for that population, based on the design.

DR. BURMAN: Thank you. In summary of this, there's some consensus and some not consensus. The consensus is that secondary prevention seems to be a more substantiated benefit than primary prevention. However, there was some debate about that, and some people thought it should be approved for both primary and secondary.

The age, there wasn't any consensus. My view is that it should follow pretty closely to

PROVE-IT, to the study; but on the other hand, that would limit it to patients who are 45 or older. It would limit it to people with an LDL of 100 or less. And the triglycerides, do they really have to fall into the 150, or so, to 500 range? I would say that I personally would expand that, but from a consensus standpoint, I'd say -- and it's hard to tell -- most of the people thought the age should be consistent with the studies.

The diagnosis of diabetes should be included. For people who don't have known heart disease, there should be an additional risk factor for CVD. The LDL concentration, we didn't talk about too much, but should be controlled, at least 100 or less. Plasma triglyceride concentrations should vary, though we didn't talk about it that much. The minimum should be probably 150 to 200. You can take a pick, but should it really stop at 500 or 499? That's a difficult question.

Intensity of statin therapy we seem to agree on. I don't think there were other necessary factors. But I think there is a basic question of

how much do you expand the indications, or recommendations for the indications, when the study included people of a certain age, when pathophysiologically, as was said, if someone's 35 and not 45 or 50, will they benefit from the drug, and should you inhibit them from getting easy access to it?

I'd appreciate any comments on that.

DR. KONSTAM: Well, I think what you said was really good. I want to just get clarification on something that Dr. de Lemos said, just to be sure I know. The drug is presently approved for patients who have elevated triglycerides and have diabetes.

(Crosstalk.)

DR. DE LEMOS: Just elevated triglycerides.

DR. KONSTAM: Wait. I'm sorry. What?

DR. BURMAN: It's approved for very --

DR. KONSTAM: So it's a very high triglyceride level, so it's not approved in this population. Okay. Thank you.

DR. BURMAN: Okay.

MS. McCOLLISTER-SLIPP: Anna McCollister. Just a minor point, and again, I'm here speaking from the consumer/patient perspective. The more prescriptive we are in recommending to the agency that they create a label that's very prescriptive, based very strictly on the design of this specific trial, the more difficult it's going to be for patients to get it.

Insurance companies, God bless them, have a way of looking at the exact wording of an FDA guidance document or indication, and using those as mechanisms for denying coverage. I've had to fight so many battles.

(Applause.)

MS. McCOLLISTER-SLIPP: I was not expecting that, but anyway, I've had to fight so many battles. And these are really significant burdens on patients. It's a lot of time, it's a lot of heartache, and these are people who have jobs and lives. I take 16 different meds, so that's a lot of hoops to jump through.

So the more prescriptive we are, I mean, 45

seems like a pretty arbitrary number. I know you've got to pick something when you're designing a study, but that doesn't mean that we have to choose the same seemingly arbitrary number in recommending to the agency what the indication should be.

DR. BURMAN: Thank you. Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. I just wanted to add a clarification. I think there was no difference seen in patients with or without diabetes in terms of benefits, so I don't think that it has to be in patients with diabetes, as long as they have established ASCVD. I think that was one clarification, but the other is I think the labeling has to reflect the available evidence. Even though I think access to therapies is incredibly important, it also has to reflect the data that we have.

Lastly, the population that I was talking about, CV risk category 2 from the start had 2400 patients, but only 2000 actually do not have established ASCVD. So that's the difference in

population I'm talking about here.

DR. BURMAN: Thank you. Now, we have a question for the panel. There was some discussion that some people want to break for 10 minutes and some people don't. Obviously, a break for 10 minutes isn't always 10 minutes, and it may delay us past 5:00, and people have flights and other things.

So in the spirit of democracy on the committee, who would like to take a break?

(Laughter.)

DR. BURMAN: So I won't ask who. I get the impression that there's unanimous consent to go ahead with the voting questions, but, of course, if someone wants to take a quick break and come right back, they're welcomed to do that.

Does the committee agree?

(Affirmative nods.)

DR. BURMAN: Good. Then let's forge ahead with the voting question.

We will be using an electronic voting system for this meeting. Once we begin the vote, the

buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will please state their name and their vote into the record, and please state the reason why you voted as you did. We will continue in the same manner until all comments have been made or all questions discussed.

Does the FDA have any other specific instructions prior to the vote?

(Dr. Yanoff gestures no.)

DR. BURMAN: No? Then I will read the question.

Has the applicant provided sufficient

evidence of efficacy and safety to support the approval of Vascepa for an indication to reduce the risk of cardiovascular events? If yes, please provide your recommendation regarding the indicated population and components of the primary endpoint to include in labeling. If no, please provide your rationale and comment on what additional data would be needed to support the approval.

I believe we're ready to vote. Does anybody have any specific clarification they need on the vote?

DR. KONSTAM: Is there one question here? Are there three questions? Are we voting three times or this is all just one question?

DR. BURMAN: One question.

DR. KONSTAM: So A and B is for commentary.

DR. BURMAN: Yes. Any other clarifications?

DR. KONSTAM: I'm slow, but I've got it now.

DR. BURMAN: No problem. Okay. Please vote.

(Voting).

DR. BURMAN: We're getting Dr. Posner's

vote.

DR. FAJICULAY: For the record, the results are 16 yes; zero no; zero abstain; and zero no vote.

(Applause.)

DR. BURMAN: Thank you very much. Thank you for your help. We will now go around the room. Please, starting over here for the voting members, and state your name and your vote into the record, and your explanation.

DR. CHRISCHILLES: Elizabeth Chrischilles from the University of Iowa, Department of Epidemiology. I voted yes, as we all did. I can't remember exactly the rest of the prompt, but I think the indications that reflect the inclusion and exclusion criteria to the study would be the appropriate approval level. Beyond that, I'm not comfortable. I'm a little bit less sure about the need for an age limitation, as it seems like there could be some, really, substantial potential benefit right around that -45 or 50-year age threshold.

DR. YANOVSKI: Jack Yanovski. I voted yes, as everyone else did. We all agree that the primary study showed substantial benefit. I think the design of the study left us with questions about exactly who would most benefit; clearly those with established cardiovascular disease benefit; and it's quite possible that a substantial portion of those with diabetes, who have, therefore, a high risk for development of cardiovascular disease plus additional risk factors, including hypertension; and certainly they all have dyslipidemia.

All treated with statins would be the appropriate group. The age cutpoint somewhere around 40 is probably going to be the right number. And indeed, we have to think carefully about whether the triglyceride level will be a necessary additional factor or not because it's not clear at all whether there's a better cutpoint to be used.

Whether there can be a limitation according to cardiovascular risk, the analysis I was shown was not sufficient. to my mind. It may will be that you'll see the most benefit in those who have

1 even higher risks than a 10 percent risk. But I
2 think that there was no doubt that this was a
3 medication that could benefit a substantial portion
4 of the U.S. populace and meet an unmet need.
5 DR. ORTEL: Tom Ortel. I also voted yes for
6 all of the same reasons that were mentioned. I do
7 think that there does need to be postmarketing
8 surveillance on the bleeding issue. I think we
9 need to know more about that. I also do have some
10 concerns about opening this up for primary
11 prevention broadly, only because, as we talk about
12 people, as has been mentioned, who have less risk
13 for an adverse outcome, the bleeding event rate is
14 still potentially there and can be a bigger
15 problem.
16 DR. NASON: Martha Nason. I voted yes. I'm
17 won over that this is effective, even despite the
18 problems with the mineral oil placebo for a
19 secondary prevention in established cardiovascular
20 disease. I'm definitely more on the fence on
21 primary. I think we all are. I think there's a
22 judgment call there, and if primary is included,

it'll have to stick to who was in the study and be a sort of narrow-ish indication for primary prevention.

On the other hand, I think my best case scenario would be -- I know saying do another study is much easier said than done, but I would love to see it with a different placebo, please, and maybe a wider net as to who would be high risk primary, so maybe even if you don't have diabetes, but you have metabolic syndrome and other high risk factors other than that, in order to really broaden that label into primary prevention, assuming it held up.

MS. McCOLLISTER-SLIPP: Anna McCollister, consumer representative. I voted yes because I think the benefits are significant. I think the safety is pretty strong. I think bleeding is a real issue, but it's one that can be watched and monitored. And relative to the risks of cardiovascular events, um, more broadly speaking, I think it's far more manageable. The more options we have, the better it is for patients.

I would ask that the agency think very close

or give significant thought to how prescriptive they're going to be in the labeling, just because this really does create a significant burden and workload for patients, as well as physicians. As I said previously, the study age was a relatively arbitrary number. If you're one year under that, it still creates a restriction and a barrier.

I'd love for somebody to do a study of the cardiovascular effects of insurance appeals --

(Laughter.)

MS. McCOLLISTER-SLIPP: -- but putting that aside, that's, anyway, my thoughts.

DR. KONSTAM: This is Marv Konstam. I voted yes. So the issue really is do we break down the population. My inclination is not to break down the population on two grounds. One is statistical grounds. There's a clinical trialist, it's one trial, and that's really what you know, and subgroups are subgroups. But from a biologic perspective, I dare say that everybody in the trial -- or the vast majority people in the trial probably have the disease. If you did

intravascular ultrasound, or if you looked at endothelial function, I dare say you'd see abnormalities in a large proportion of the patients who we're calling primary prevention.

So the difference between the two is they haven't had events yet, so I'm more inclined on both perspectives not to split the population. However, I think it's a close call, and I think that risk mitigation -- I'm sorry. The net clinical benefit thing, I think that the FDA really needs to stare carefully at the net clinical benefit in the lower risk, quote, "primary prevention population."

I think with regard to the -- one other point about groups that didn't -- I think somebody said patients have to be on maximum statin therapy, maximum tolerated statin therapy. I will remind you that, again, having said what I said about subgroups, there is no evidence that it works in patients with very low statin doses. There was actually a non-statistically significant qualitative difference in that group. So I think

that's something that should be represented in the labeling.

Then finally, risk mitigation with regard to bleeding, one question that comes up, and this is a very long half-life, is should this drug be stopped if you're contemplating elective surgery? I don't know. There is an increased risk of bleeding, and we stop other anticoagulants, and this has an anticoagulant effect.

So I think that's the question that clinicians will want to answered, and it would be a very long stoppage of the drug if you're talking about that. So that's another specific point, but anyway, that's summarizes my comments.

DR. WEBER: This is Tom Weber, and I voted yes. I believe the clinical data, based on this well-designed, single clinical trial, which I do think is sufficient, affirms the drug for approval for secondary prevention of cardiovascular events in patients with existing atherosclerotic disease.

I would not recommend the inclusion of prevention of cardiovascular death and indication

1 based on the data. I would not also recommend an
2 indication for primary prevention of CV events
3 based on the data presented to date. I believe
4 there's insufficient data to establish a primary
5 prevention population that will truly have adequate
6 and acceptable benefit more than risk, particularly
7 given concerns over the robustness of the
8 therapeutic effects in the primary prevention
9 population versus the risk of bleeding and atrial
10 fibrillation.
11 DR. NEWMAN: Connie Newman. I voted yes.
12 Even though I had some concern about the placebo
13 arm, I felt the benefit-risk was overwhelmingly
14 favorable. I think that the population who could
15 be given the drug should be adults over the age of
16 40 on maximally tolerated statin therapy or other
17 lipid lowering therapy, with atherosclerotic
18 cardiovascular disease or with diabetes, and with
19 plasma triglycerides greater than 150.
20 DR. WILSON: Peter Wilson. I voted yes. I
21 voted just like Dr. Konstam, with asterisks. I
22 think we have a very clear signal for secondary

prevention, for yet another event, but it's not quite strong enough, even overall, when we take it for cardiovascular death, and then you have to go back to the entire trial. So we still have some gaps.

I am concerned, as a lipidologist, about will more than the target group get this medication because I'm not sure it really provides much benefit over and above our guideline driven therapy with maximally tolerated statins for persons with moderately high triglycerides. That's what it says right now in the current guidelines.

The idea of developing with the sponsor -- especially this primary prevention group was diabetics with multiple risk factors, more than one, but, actually, we heard -- that was very helpful, diabetics with two risk factors, and high risk as shown by the sponsor's presentation. So maybe that could get refined and made more usable before labeling is determined.

The final comment is we have an awful lot of hyper triglyceride patients in our clinics, younger

1 people, non-diabetics who may not benefit at all
2 from this, and we should be careful. They don't
3 necessarily need this medication at all, so we
4 should be thoughtful about that as we go forward.
5 DR. ELLENBERG: Susan Ellenberg. I voted
6 yes. With all the caveats, I'm still comfortable
7 with this being approved for both primary and
8 secondary prevention. I think that if there's
9 sufficient hesitation in the community about the
10 primary prevention indication, that may show up in
11 terms of reluctance to prescribe it. There might
12 be a motivation, then, to do another trial. I
13 think it would be ethical to do another trial, even
14 if the drug is approved, and I think there are
15 certainly examples where that's been done in the
16 past.
17 I think it would be a good idea to have some
18 kind of postmarketing study, maybe an observational
19 cohort. There is a troublesome a history, as we
20 all know of learning after approval, that whatever
21 estimate we made of a certain adverse event, it was
22 often very much underestimated in the trial. Once

it gets out and is widely used, we find that there are more people that have this. So I think it would be good to have more study of this.

With regard to the limits, on age in particular, I can see both sides of it. I'm not terribly comfortable in going beyond what was used in the study. There are a lot of issues that I'm not sure I really am qualified to consider. I would leave it to the FDA to determine whether there should be some expansion for some of these categories.

DR. BURMAN: Ken Burman. I voted yes. With regard to the indications, obviously, it's difficult to know for sure. My recommendation is that it be approved for primary and secondary prevention; also that the strict age guidelines in the study maybe could be expanded. Obviously, we don't want to neglect someone who's 40 or 35 who has known cardiovascular disease and may benefit from this drug, this agent. I think the LDLs should be well controlled less than 100, and I think the triglycerides should be probably 150 and

above, and then how much above is debatable. The study said 499, and I could go with that.

We haven't really spoken about exclusion factors, but I'll mention that in the study, liver disease, severe congestive heart failure, A1c greater than 10 percent, significant hypertension, and creatinine clearance less than 30, all were exclusion factors, and those seemed reasonable. The patient shouldn't be on other anticoagulants, or fibrates, or niacin, and shouldn't be taking a PCSK9 inhibitor at the same time.

That having been said, my general comment, in summary, is that there is definitely an increased cardiovascular risk in patients taking statin who have even reached goal LDL. There's a definite need for additional therapeutic approaches. The study supports the use of icosapent ethyl to further reduce cardiovascular events. It appears effective and safe.

The increased risk of atrial fibrillation, and atrial flutter, and bleeding events can be potentially recognized with education of the

patient and physician, and managed appropriately -- others may a little bit; that the mechanism of action of icosapent ethyl and cardiovascular decrease is not clearly defined. However, in summary, this seems a very useful new agent as an addition to the armamentarium for the treatment of these patients. Thank you.

DR. KRAFT: Walter Kraft. I voted yes. The elements that informed that were, albeit one study, one that was large with a large degree of internal validity, and I would argue a large amount of external validity. There was favorable safety profile, and this one paired with an unmet medical need has the potential, given the number of people with the underlying condition, to have a large societal impact.

The indication of secondary prevention is clear. For primary prevention, I would argue that there is also not a risk for extending too far, but not extending the indication far enough when you think about the societal need. For that reason, I would suggest for primary prevention, to limit

mostly within the confines of the inclusion/exclusion criteria.

DR. LOW WANG: Cecilia Low Wang. I voted yes. I do think that the applicant provided sufficient evidence of efficacy and safety to support this indication to reduce the risk of cardiovascular events. I think that the labeling -- first of all, I think the indicated population should be limited to patients with established ASCVD. I'm not convinced that the data support the primary prevention cohort.

I also think that patients need to be on maximally tolerated statin and have triglycerides of over 150. I think the labeling needs to include caution for patients with a history of Afib or Aflutter, as well as patients who are on antithrombotic or anticoagulant therapy for the increased risk of bleeding, but I would love to see -- I don't know if this would be possible -- a randomized-controlled trial in the primary prevention cohort.

DR. DE LEMOS: This is James de Lemos. I

voted yes. This is an extremely well-conducted and important trial that meets an unmet clinical need. I would limit this indication for CVD risk reduction in patients with established atherosclerotic vascular disease. I find if the bar is to take a modest size subgroup and show the lack of statistical heterogeneity, when that subgroup is fundamentally different, meaning primary prevention, that's a very low bar in my view. I look forward to an adequately powered study in primary prevention because I think the drug has
great promise there as well.

DR. BRITTAIN: Erica Brittain. I voted yes. Obviously, there was very strong efficacy shown across all subgroups, or almost all groups. The mineral oil was something that worried me. I'm not 100 percent convinced it's not an issue, but I'm enough convinced that the effect was probably minimal. I do think the indication should match the trial entry criteria.

I do think the issue about the primary

prevention is debatable, as we have debated it. The treatment effect was still pretty good in that group, so that gives me comfort. It wasn't powered to be significant. It has a low event rate, so it's going to be hard to be significant.

That said, I think it's sort of an interesting philosophical question. Just because you include a group in your study doesn't mean that we can now say it works in everybody that's included. I think we have to be honest about that. So perhaps the wishy-washy in between is to look at that risk-benefit in the patients at lowest risk, or at least highlight the potential issue with risk-benefit in the patients with lowest risk in the label.

DR. BURMAN: Thank you. Dr. Posner, on the phone?

DR. POSNER: Yes, I'm here.

DR. BURMAN: Please continue. Thank you.

DR. POSNER: Yes. I voted yes, and I'd like to agree with Dr. Weber, Konstam, Wilson, Wang, and de Lemos in their concerns. I have very similar

concerns in that we have a drug with no known mechanism; a large amount of percentage data versus actual numbers as to what is happening; and low power in the primary prevention group. My fear as a patient is I don't want to see this become what I call cardio candy, so that at 10:00, 11:00, 12:00 at night, you see ads of people saying their lives were saved and everybody should be taking it, because it's a wonder drug.

I think it's important for the group that it's been proven to work on in this study, which was done very nicely, but expanding it to a point where everybody thinks they should be taking it, and it's going to keep them alive without adverse events is a dangerous step. Warnings need to be put into the labeling so the doctors aren't overselling it, that patients aren't overdemanding it, and that the people that really need it are able to get it approved by their insurance companies. Thank you.

DR. BURMAN: Thank you.

Thanks to everyone on the panel. Are there

any final comments from the FDA?

DR. SHARRETTS: Hi. John Sharretts. No, we do not have any further questions.

Adjournment

DR. BURMAN: Thank you. I would like to thank all members of the panel. I'd like to thank the FDA and the sponsor for wonderful presentations and their ability to answer questions. I'd like to thank especially the OPH members and their discussions.

Panel members, please take all personal belongings with you, as the room is cleaned. Please leave your name badge on the table. All of the materials may be left. We will now adjourn the meeting. Thank you.

(Whereupon, at 4:28 p.m., the meeting was adjourned.)