FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC)

Wednesday, October 18, 2017

8:06 a.m. to 4:53 p.m.

Thomas Douglas Conference Center

10000 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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C O N T E N T S

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P R O C E E D I N G S

(8:06 a.m.)

Call to Order

Introduction

DR. WILSON: Good morning. I'd like to remind everyone first as we begin this meeting to silence your phones and any other devices that may become audible. We have a variety of things that I am instructed to inform you of as we start up.

First, we have an FDA press contact, Theresa Eisenman.

Is Theresa in the room? Do you see her? She's coming later. When she comes, we'll let you know, okay?

I'm Peter Wilson. I'm the chair of the Endocrinologic and Metabolic Drugs Advisory Committee, and I'll be chairing the meeting today. I'm calling the meeting to order. We'd like to first start by going around, introducing ourselves. We're going to start to the far left with FDA. Thank you.

DR. THANH HAI: Good morning. I'm Mary

Thanh Hai. I'm the deputy director in Office of Drug Evaluation II.

DR. SMITH: Good morning. I'm Jim Smith, deputy director, Division of Metabolism and Endocrinology Products.

DR. CHONG: Good morning. William Chong, clinical team leader, Division of Metabolism and Endocrinology Products.

DR. LUNGU: Good morning. Andrea Lungu, clinical reviewer, FDA.

DR. HSUEH: Ya-Hui Hsueh, statistical reviewer, Office of Biostatistics.

DR. NEATON: Jim Neaton, professor of biostatistics, University of Minnesota.

DR. EVERETT: Brendan Everett, cardiologist at Brigham and Women's Hospital in Boston and assistant professor at Harvard Medical School.

DR. LOW WANG: Cecilia Low Wang, associate professor of medicine at the University of Colorado.

DR. WEBER: Tom Weber. I'm an endocrinologist at Duke University Medical Center

in Durham, North Carolina.

DR. DEL PRIORE: Luciano Del Priore. I'm at the Yale University School of Medicine, a professor in the Department of Ophthalmology.

DR. ROSENBERG: Good morning. I'm Yves Rosenberg. I'm a branch chief at the National Heart, Lung, and Blood Institute and preventive medicine physician, clinical trialist.

CDR BONNER: Good morning. LaToya Bonner, DFO for EMDAC.

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

DR. BUDNITZ: Good morning. Dan Budnitz, medical officer with Division of Health Quality Promotion at CDC.

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

MS. ROBOTTI: Sue Robotti, founder of MedShadow Foundation and executive director of DES Action, consumer rep for Drug Safety and Risk Management Committee.

DR. LUMLEY: Dan Lumley, patient representative from Kansas City.

DR. LI-NG: Melissa Li-Ng, endocrinologist from Cleveland Clinic.

DR. BLAHA: Hi. Mike Blaha, I'm associate professor of cardiology and epidemiology, Johns Hopkins Ciccarone Center for Prevention of Heart Disease.

DR. YANOVSKI: Susan Yanovski. I'm co-director of the Office of Obesity Research at the National Institute of Diabetes and Digestive and Kidney Diseases.

DR. HIATT: William Hiatt. I'm a professor of medicine, University of Colorado, Division of Cardiology, and I run a clinical trial center for the university.

DR. PALEVSKY: Paul Palevsky. I'm chief of renal at the VA Pittsburg Healthcare System, professor of medicine at the University of Pittsburg, and nephrologist.

DR. FERRIS: I'm Rick Ferris, ophthalmologist, director of Division of

Epidemiology and Clinical Applications, National Eye Institute.

DR. SLEEP: Good morning. I'm Darryl Sleep. I head the U.S. medical office at Takeda Pharmaceuticals.

DR. WILSON: Okay. Thank you very much.

For topics such as what we'll be discussing today, there are a variety of opinions, some of which are 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. And 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, back to you, Commander Bonner.

Conflict of Interest Statement

CDR BONNER: Good morning. 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 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 discussion 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 is involving a discussion of the safety and efficacy of New Drug Application 209637 for semaglutide injection submitted by Novo Nordisk as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

This is a particular matters meeting during which specific matters related to Novo Nordisk's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee 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. Darryl Sleep is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Sleep's role at this meeting is to represent industry in general and not any particular company. Dr. Sleep is employed by Takeda Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. WILSON: We're now going to first have an FDA presentation, and that will be done by William Chong. And then it will be followed by our

guest speaking, Dr. Emily Chew from the Eye Institute.

Dr. Chong?

FDA Introductory Remarks - William Chong

DR. CHONG: Good morning. My name is William Chong. I'm a team leader in the Division of Metabolism and Endocrinology Products at the FDA. I'd like to welcome the advisory committee panel, Novo Nordisk, and members of the public to today's public advisory committee meeting.

Diabetes mellitus is a serious chronic disease that affects over 30 million people in the United States. The majority of these patients have type 2. Patients with diabetes have an increased risk for micro and macrovascular complications. And the current goal of therapy is to improve glycemic control with the intent of reducing the risk for these complications, which include things like diabetic retinopathy, nephropathy, and neuropathy.

Data supporting that improved glycemic control leads to improved clinical outcomes come

from large prospective clinical trials such as the DCCT, which compared intensive therapy with conventional therapy in patients with type 1 diabetes. The primary objective of this study was to evaluate whether intensive therapy reduced progression of diabetic retinopathy, and they looked both at primary prevention and secondary prevention.

The intensive therapy group achieved better glycemic control with the mean hemoglobin A1c of 7 percent compared to 9 percent in the conventional therapy arm. This difference in glycemic control translated into a reduction and the risk of diabetic retinopathy progression. Starting at three years, the intensive therapy group showed a benefit compared to conventional therapy, and this was true both in primary prevention and in secondary prevention.

The UKPDS was another large trial that compared intensive therapy with conventional therapy. This trial was conducted in patients with type 2 diabetes. The primary objective of this

study was to see if intensive therapy prevented complications. The intensive therapy arm achieved better glycemic control with a hemoglobin A1c of 7 percent, while the conventional treatment arm had a mean hemoglobin A1c of around 8 percent. At 10 years, this resulted in a 25 percent risk reduction for microvascular endpoints mostly due to fewer cases of retinal photocoagulation.

We currently have 12 classes of drugs approved to improve glycemic control. Today, we're here to discuss a proposed new member of the GLP-1 receptor agonist class, highlighted here. Through binding and activation of the GLP-1 receptor, GLP-1 receptor agonist increased glucose-dependent insulin secretion, delayed gastric emptying, and inhibit glucagon secretion. This, in turn, has been shown to lead to improved glycemic control.

The proposed drug product that we're discussing today, semaglutide, is a once-weekly, GLP-1 receptor agonist that, if approved, will be the seventh member of the class.

Today, we'll be hearing presentations that

will discuss the findings from the development program for semaglutide. This program included eight phase 3 trials, of which one of them was a two-year cardiovascular outcomes trial.

We'll be hearing presentations that cover both the efficacy findings and the safety findings, and of those safety findings will include the discussion of the assessment of cardiovascular risk and findings for diabetic retinopathy complications.

Our agenda for the day is summarized here. We'll be beginning with presentation from Dr. Emily Chew from the National Institute of Health on diabetic retinopathy. We'll then hear presentations from Novo Nordisk, and then turn the presentations from the FDA. There'll be time for questions after each of these presentations. We'll then take a break for lunch, and after we return, we'll have an open public hearing, and we'll follow with discussion questions to the panel.

Turning to the questions that we have for the panel, our first question is one on efficacy of

semaglutide. Semaglutide is proposed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. We'd like you to discuss the efficacy of semaglutide with respect to glycemic control.

Our second question for you to discuss is on safety. Semaglutide once-weekly injection has been studied in seven phase 3 studies and a two-year cardiovascular outcomes trial. Excluding issues related to diabetic retinopathy and cardiovascular risks, we'd like you to discuss any safety concerns you have related to semaglutide.

Our third question focuses on the diabetic retinopathy findings and include several parts. In SUSTAIN 6, a prespecified secondary safety endpoint was time from randomization to the first occurrence of either a need for a retinal photocoagulation, need for treatment with intravitreal agents, vitreous hemorrhage or diabetes-related blindness. The results for this composite endpoint showed an increased risk with semaglutide with a hazard ratio and confidence interval shown here.

We'd like you to first discuss the strengths and limitations of this assessment, including comments on the endpoint definitions, methods of ascertainment, adjudication, trial design, and any other considerations that you believe relevant to the interpretation of the results.

After that, we'd like you to discuss one of the hypotheses regarding the finding. One hypothesis regarding this finding is that rapid and large reductions in hemoglobin A1c can be expected to increase the short-term risk of diabetic retinopathy complications. We'd like you to discuss the extent to which you are convinced that a reduction in blood glucose is a mediator of the observed increase in diabetic retinopathy complications in SUSTAIN 6.

Next, we'd like you to discuss your assessment of the clinical benefits given the findings of the retinopathy complications. Improving glycemic control should be expected to reduce the risk of retinopathy over the long term, and we'd like you to discuss whether the increase

in diabetic retinopathy complications in a two-year controlled trial affects your assessment of the clinical benefits expected from long-term use of semaglutide.

Part 4 of this question is shown here. In SUSTAIN 6, the increase in absolute risk of diabetic retinopathy complications was greater among those with diabetic retinopathy at baseline compared to those without diabetic retinopathy at baseline although the relative risk increases were similar.

Patients with diabetic retinopathy are among those most in need of improved glycemic control, and we would like you to discuss whether you would have any concerns about the use of semaglutide among patients with diabetic retinopathy. The last part of this question is we'd like you to comment on your level of concern related to the observed increased risk in diabetic retinopathy complications in SUSTAIN 6.

Our fourth question is about cardiovascular risk and the cardiovascular risk assessment for

semaglutide. In SUSTAIN 6, a total of 254 first MACE occurred during a median two-year follow-up. The estimated hazard ratio of MACE and the components of MACE for semaglutide versus placebo are shown here. We would like you to discuss these results and comment whether these data are adequate to characterize the cardiovascular safety of semaglutide.

Our last question will be our voting question. We would ask you to consider whether the available efficacy and safety data support approval of semaglutide 0.5 milligrams and 1 milligram administered subcutaneously once weekly as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

The reasoning behind your vote is as important as your vote, so we'd like you to comment, if you vote yes, to explain your rationale and comment whether any additional studies should be required after approval. And if you vote no, we'd like you to describe what further studies you believe should be conducted to establish a

favorable benefit-risk to support approval.

Thank you again for your participation today, and we look forward to an informative discussion.

Now, I would like to introduce our guest speaker from the National Institute of Health. Dr. Emily Chew is the deputy director of the Division of Epidemiology and Clinical Applications and is also the chief the clinical trial branch of that division at the National Eye Institute in Bethesda, Maryland.

Dr. Chew received her medical degree in ophthalmology training at the University of Toronto and has served as an assistant professor there before joining the National Eye Institute. Her research interests include clinical trials in epidemiologic studies in retina vascular disease such as age-related macular degeneration and diabetic retinopathy. She has extensive experience with several large multicenter trials, including the Age-Related Eye Disease Study 2 and the ACCORD Eye Study.

Dr. Chew, thank you for coming to speak today and sharing your expertise.

NIH Presentation – Emily Chew

DR. CHEW: Thank you very much, Bill. It's a pleasure to be here. I understand that I'm supposed to fill in some gaps in terms of the knowledge of diabetic retinopathy. It's my pleasure to present this. I have no financial disclosures.

I'm going to really just talk about the classification, how we came about, to talk about diabetic retinopathy, and what we use for clinical trials, and why it's so important. Some of the risk factors, I'm going to really talk about clinical trials only. The observational data were very strong, but even more important is the gold standards from all the clinical trials. You just saw some of it from Bill's talk already.

Most of the work that we've done has been done on diabetic retinopathy based upon fundus photographs, which are documenting various lesions in the retinopathy. And this has been about four

or five decades of research, which has really allowed us to look at diabetic retinopathy in a very orderly way.

It progresses very similarly and in all patients. We do this with stereoscopic fundus photographs, looking at the retina, and now we even have larger, 200 degrees -- this is only a small fraction of what we can actually look at.

The five pathological processes, first is the microaneurysms, and we've foreseen that, and it leads to vascular permeability. These small vessels, endothelial cells in the retina are very much like the blood-brain barrier; they do not allow things to come through. But when it becomes leaky, we have permeability issues that causes problems such as macular edema, vascular occlusion takes place. And then when this gets really ischemic, new blood vessels grow, and of course with new blood vessels, fibrous proliferation goes along, and there's contraction and causing scarring.

Classification is really very simple. It's

mild, or moderate, and no apparent retinopathy even though there might be some things going on histopathologically, but we cannot see anything. And this goes on to, as you can see in this picture, showing the normal, in your left-lower quadrant, the blood vessels that have no changes. But the diabetic changes have these microaneurysms that are blown up, and you see they're just out-pouchings of these vessels that leak.

Early signs are just -- blood vessels that have -- hemorrhages that have no impact on vision; this patient is 20/20. But the vascular permeability causes these hard exudates to come out, these lipid deposits, causing macular edema. The patient has compromised vision. They cannot drive without a restricted license.

Here, we see fluorescein angiograms showing the leakage of these blood vessels that causes this macular edema, which is a major cause of blindness. And again, we see these signs of hard exudates, and you will see when you look in.

When we do a histopathology, we actually see

lipid deposits within the retina. This is the oil red O showing lipid in the eye. And again, the blood vessels then occlude, and you get to a point where you have lots of signs of severe non-proliferative disease. In other words, the blood vessels are closing down, and these are some of the signs that we look for.

Then finally, we have new blood vessel proliferation which you see, really, terminal end stage that causes a lot of problems, visual acuity loss, hemorrhages, and scarring, and then retinal detachment can occur.

Because it's so orderly, we can actually look at this in a very standardized way. This is the ETDRS, Early Treatment Diabetic Retinopathy Study, which has been refined over a number of decades. We have 17 steps to look at this using both eyes, so we don't look at vision as our final outcome but this progression along the scale, which is very important. It's allowed us to do studies in a smaller number of patients and not using visual acuity.

Visual acuity is more difficult because our treatments are actually highly effective these days, so to have vision loss would be very difficult. You would need tens of thousands of patients to do that.

I'm going to focus on the medical risk factors, blood glucose, blood pressure, and blood lipids. You heard some of this already, the DCCT, the iconic study that was supported by NIH in type 1 diabetes. And this study, I'd like to remind you, was sample sizes based upon retinopathy. The eye findings was the primary outcome in this study.

Primary prevention are those patients who have no eye disease, no retinopathy. Secondary intervention are those who already have retinopathy when they came in the study. If they have the disease, it's a horse out of the barn, can we still do further. And you heard already, will intensive therapy prevent the development and subsequent progression of retinopathy in the primary prevention? And the second prevention, or those

who already have it, will it prevent the progression of retinopathy?

It was very well done. You can see there was a nice separation of the A1c levels between the conventional and intensive group, and this persisted for six and a half years. But what was surprising was the first year. I know from my colleagues who were on the DSMC study that almost sunk the study because they saw this early worsening of the retinopathy.

The tight control group had more progression along this three-step scale that we talked about. It was worse in the standard care, and this persisted at one year. This is the primary prevention. This also occurred in the secondary prevention. There was this worsening of retinopathy. I'll say a few words about this later in another publication I will go over.

In 2 years, it starts to narrow down, and this is primary and secondary. But then when you look at the long term, long-term effects is that intensive control far outweighs the standard care.

And that's like a little blip in the actual life of the retinopathy. We have as much as 76 percent prevention from progression, so this is a very powerful treatment. Secondary, even if you have the disease, over time, by about three years, you start seeing a separation. Clearly, glycemic control has a huge impact on progression of retinopathy.

The results of the DCCT suggests there's early worsening from the first to second year, it's rather transient, and numbers of reduction in retinopathy progression. And this is clinically important by 34 to 76 percent reduction by intensive control. Photocoagulation was used by almost a third, and the first appearance of retinopathy was reduced by 27 percent.

This early worsening occurred within the 12 months, and every 6 months, we were actually looking at these patients, which is pretty intense. We don't do that anymore because we know progression doesn't go that quickly.

In this paper in 1998, they looked very

carefully at this early worsening. And what we found in this case was that it was a doubling. As you see, there's a doubling of the odds ratio. For people who were in the intensive group, it was 13 points, 1 percent who had this early worsening versus 7.6 in the conventional group; not much different from what we saw earlier from the current study here. Recovery has occurred in the 18 months, so they get better and there's really no difference.

The KROC study is another study which looked at intensive control, and this was done in only 68 patients. This was a continuous subcutaneous infusion of insulin versus an unchanged conventional injection treatment. You can see that was accelerated. Within 8 months, there was an accelerated progression of diabetic retinopathy, but by 2 years, they were again similar. This early worsening was very familiar to all of us, at least in diabetic retinopathy research. I think what's remarkable is this glycemic control continues to be very important.

The EDIC study, which is the extension of the DCCT, Epidemiology of Diabetic Intervention and Complications Study, looked at the natural history following the cessation of the clinical trial. It shows the beneficial effect of these tight control that goes on to 4 to 23 years, so its so called legacy effect or metabolic memory persists.

You can see here, I've put together the DCCT A1c levels. This is 6 and a half years during the DCCT. In the EDIC study, by 10 years, you can see that the A1c level are almost equal, or they are equal, 8.0 in both arms. And they actually really go towards a very similar number.

Even at 4 years, there was a reduction in progression retinopathy, development of important retinopathy that causes vision loss, macular edema development, and laser was also reduced still even though the patient's A1c level was becoming closer and closer together. This persists for at least 10 years, and this is following the stopping of the control.

This legacy effect wanes over time. At

4 years, it's stronger, but by 10 years, it's a little bit less. But nevertheless, that persists. Even at 23 years, those who had intensive glycemic control, 23 years later, had less ocular surgery, so this is a very powerful treatment.

At 30 years, David Nathan has brought a very nice paper talking about the importance of the results. You heard a bit about the UKPDS already; it's a type 2 diabetes. This looks, again, in intensive glycemic control. These patients have been just diagnosed within the past year. This is 4,000 patients who are randomized to conventional or intensive group. And you see the A1c level actually goes up over time, but there's a nice separation between the two treatment groups. This is a composite outcome of the microvascular endpoints. Here, we see that there is a slightly difference in terms of the microvascular outcomes.

This is retinopathy. We only saw patients every three years; at least, they were only photographed every three years. We were not worried about the transient early effect because we

know that it got better. In the core study, for example, we did it every four years for that same reason. And this, you can see that, again, there was a microvascular outcome that was really pretty significant. There was a good reduction with the intensive therapy.

Blood pressure was also found to have a positive effect. Having really just a small modest effect in their reduction in their blood pressure, there was an effect on diabetic retinopathy.

I briefly touched upon the ACCORD Eye Study, which is a more recent study on type 2 diabetics, and these are patients who had duration of 10 years who have had a cardiovascular risk as well. And the primary outcome, of course, is to look at the cardiovascular disease. We were aiming for a very intensive glycemic control, less than 6 versus 7.9 percent. We also looked at fenofibrate and simvastatin versus placebo, and simvastatin to look at the treatment of dyslipidemia for prevention of diabetic retinopathy progression.

We looked at intensive blood pressure

control, which was 120 versus 140. We only looked at the subset of this group because we didn't need all 10,000 patients based on the fact we have the scale which allowed to have some economy of power and funds.

The final outcome was with tight glycemic control, the odds ratio was 0.67, highly statistically significant for reduction of progression of retinopathy of 3-step, or having vitrectomy or laser over a period of 4 years. And the same was the fenofibrate 0.6, and for blood pressure, we didn't make a difference.

This is what we see. During the course of the study, we see that the A1c level was reduced, not right down to 6, but 6.5 was our mean. We stopped the study at almost 4 and a half years because of some early changes that we found with mortality, and you can see that we switch over and A1c level increased.

We did a follow-up on these patients. And just like the DCCT, the A1c levels came together again. The follow-up in which the clinical trial

had stopped, this was more like the EDIC part of the study, where we're just looking at the natural history, and you can see the A1c level got together.

We went back to see these patients at 8 years. This is now 4 years after we stopped the clinical trial and we still see an effect, almost a 50 percent reduction in the progression diabetic retinopathy with tight glycemic control. The fenofibrate effect went away and the blood pressure effect had no change.

This legacy effect for type 2 diabetes is seen in ACCORD. It was also seen in UKPDS after 10 years. It's just really an important finding for type 2 as well. The intensive glycemic control has a huge impact on diabetic retinopathy. I think the early worsening is transient and far outweighed by the benefits of a tight glycemic control over the long haul.

The legacy effect seen in persons with type 1 and type 2 diabetes, indeed, it was very important, and it's just like having money in the

bank if you can get the patients in tight glycemic control for their diabetic retinopathy.

Fenofibrate treatment reduced diabetic retinopathy progression by about a third. There was no legacy effect. And I think intensive blood pressure control, we have to remember the results from the UKPDS, and in other studies such as the SPRINT, that blood pressure control is obviously very important as well.

I thank you for your attention, and if you have any questions, I'm happy to address them right now.

Clarifying Questions to Guest Speaker

DR. WILSON: Thank you very much, Dr. Chew.

Any questions for the speaker? And be sure to have those questions this morning because I believe she's going to be leaving --

DR. CHEW: At noon. At noon.

DR. WILSON: -- at noon.

DR. CHEW: Yes.

DR. WILSON: So you'll get another chance, but right now, Will Hiatt?

DR. HIATT: Thank you for that information. In preparing for the meeting and looking at some of the earlier data you showed, it appeared that sort of intensive lowering of A1c was associated with this acute worsening followed by a long-term benefit, in particularly insulin therapy, I would guess.

My question to the FDA is how is this early worsening finding labeled across different insulins? And there are a number of insulins on the market. Could someone comment on how this early risk delayed benefit is actually put in terms of how we're supposed to understand the use of drugs, particularly insulin? And is it consistent across the insulin classes?

DR. CHONG: William Chong, FDA. There is language in, I believe, all the insulin labels discussing increased risk for retinopathy when you initiate intensive therapy with insulin. I don't believe there's any language in the products approved only for type 2.

DR. HIATT: I guess my question is, it would

be helpful to know how that information is portrayed. Is it as a warning? It's not a black box, I don't think. Is it consistent across all insulins? I'm really interested in what the words say in the label, and I was trying to prepare a little bit of that before the meeting. That would be really helpful.

Is this true for all insulins? And can we just understand a little bit how you're dealing with this information, which now goes back 20 years?

DR. CHONG: I believe this is true for all insulin labels. I believe it is labeled as a warning.

DR. HIATT: Okay. And your reference says it's rapid improvement in glucose control, not necessarily unique to insulin but to any drug that rapidly improves glucose control. Is that your interpretation?

DR. CHONG: The language here does not specifically reference insulin. But again, I would note that we don't have this language in any of the

type 2 products.

DR. HIATT: Just in the insulin products.

DR. CHONG: This is just in insulin labels.

DR. HIATT: And it's consistent for all insulin products?

DR. LUNGU: Yes.

DR. CHONG: I believe so. I think it is.

DR. HIATT: Okay. If it's not, I'd be curious to know that.

DR. WILSON: Dr. Palevsky?

DR. PALEVSKY: Thank you for that excellent presentation. You showed the early worsening in retinopathy with type 1. In the studies of type 2, as I understood, there weren't data in that early time period. That's true in the ACCORD add-on?

DR. CHEW: We actually looked in ACCORD to see whether we could find anything because we only saw patients at baseline 4 years and 8 years. But we collected information on whether they got injections or laser photocoagulation. We actually took visual acuity annually at each visit, so all 10,000 patients actually had a change. There was

no change in vision.

We looked at laser photocoagulation, and there was nothing. We expected that because when we looked at the type 1 diabetes, that early worsening, there were like 3 patients who actually went on to -- 2 went on to lipid disease that needed laser and 1 had macular edema. So out of that whole group of patients, it was just a handful of patients who really had vision-threatening vision.

We tried to look in ACCORD, and we couldn't find anything. And I don't think they even looked at UKPDS because that was done very three years. I'm unsure if they collected any other information.

DR. PALEVSKY: Is there any biological reason to suspect that there would be a difference in the effect of rapid glucose control in type 1 and type 2 diabetes on retina effect?

DR. CHEW: I don't think so. Diabetic retinopathy behaves very similarly no matter type 1 or type 2. We don't really see much difference other than there's more proliferative disease

perhaps in type 1s. But when you have retinopathy, it progresses very similarly no matter where you come from, so I don't expect anything different.

For example, I think some of the studies that look at rapid control for pregnancy, for example, we've done some studies looking at that. That early pregnancy -- and partly there's a drop in control, and there's type 1 and type 2s in there, and they're all very similar. That's one place we've looked.

I think looking at the ETDRS, for example, we have both type 1s and type 2 early treatment diabetic retinopathy study, and that treatment behavior was very similar. I don't see any reason that there could be any differences between the two.

Maybe, Rick, you might have some comment on that.

DR. WILSON: Dr. Ferris, if you can help out here?

DR. FERRIS: Just a brief comment. If you look at the type 2 studies, the mean hemoglobin A1c

is around 7. The opportunity to have big reductions is lower, so potentially that treatment effect is less likely to be seen. If you look at those studies, you don't see the worsening, but you also don't see an improvement at the very earliest stage, and then it starts to improve later. So that may be a sign of potential worsening, even with that lower benefit.

Of course, there's some people with type 2 who get a big reduction in blood sugar. I don't know any study that's looked at that though. To my knowledge, nobody has any good explanation as to why this early improvement in blood sugar would lead to a worsening in retinopathy. We all have speculations, and I won't go into those.

DR. WILSON: Dr. Brittain?

DR. BRITTAIN: Thank you for your talk. I would like information about the reversibility once someone is diagnosed and any treatments. Can you speak to that at all?

DR. CHEW: We have looked at that. We actually looked at that in ACCORD, looking at

regression and progression. Of course, there's some natural here on the edge that's a part of the grading system, so we're naturally going to have some regression. You can have some regression, but it's not huge.

Now, when we do treatment nowadays with injections with anti-VEGF therapy, there definitely is an improvement in retinopathy. You actually see people not progressing and even reversing in some cases. So that's local treatment, that that's giving anti-vascular endothelial growth factor such as Avastin, Lucentis, and aflibercept, which has become a very common treatment in the injections of these drugs into the eye.

So we do see that, and that's well-documented as well, but probably less so for the glycemic control part of that. We have documented it, but it's not a huge effect, but it is there.

DR. BRITTAIN: I guess I was wondering how much extra monitoring might play a role there.

DR. WILSON: Dr. Low Wang?

DR. LOW WANG: Yes, one more question. Thank you so much for your presentation, especially for presenting the KROC collaborative study. What I was wondering is, for example, in the DCCT and the UKPDS, the baseline incidence of retinopathy is very low. Patients were diagnosed, I think, in the UKPDS, they were very early on in their diagnosis of type 2 diabetes, and in DCCT, the patients were pretty young.

What I was wondering is, is there any chance that the effect of this early worsening could have been diluted by the whole population that didn't have baseline retinopathy? So is there any study that's pulled out the patients with early worsening to see how they did over time?

DR. CHEW: How they did over time, people have looked at people with early worsening in those two studies but not in others because we haven't identified it. And your question about the retinopathy, I just want to clear up the fact that in the 1400 patients with DCCT, those 700 actually have retinopathy. Some of them have moderately

severe retinopathy. I was actually a DCCT ophthalmologist at the University of Toronto, and one of my patients progressed very rapidly. They did have patients with retinopathy there.

In UKPDS, those are days when glycemic control wasn't quite as good, and we know that a third of patients coming in with diagnosis with type 2 actually have retinopathy. And something like 4 or 5 percent may even have more severe retinopathy, so it wasn't all that pure.

When we came down to the ACCORD study, we had a lot more patients who had no retinopathy. That was 10, 15 years later, and the medical care was so much better that we expected a 40 percent progression in our ACCORD study based on the Wisconsin study, looking at some of our A1c levels et cetera. And instead of getting 40 percent, we got an 8.9 percent. So progression rates have -- and retinopathy has certainly improved dramatically because of medical care, so I think that's been part of it.

I'm not sure I've answered your question

directly, but looking at those who had early worsening, they still had a chance to not progress as much. So even if they had early worsening, they didn't go on to worse retinopathy. And most of them were very minor changes along that scale that was not vision-threatening. I think that's the other part people forget because we were looking at a 3-step change that really didn't have any true effect on the actual vision itself, if that helps.

DR. LOW WANG: If I could just follow that up, going back to looking at those patients with the early worsening and also reflecting back on a question that was asked earlier, how much of this is reversible? Have people followed those patients to see if it's reversible, and then how many patients or what percentage of patients ended up having their vision threatened?

DR. CHEW: Almost none because they are treated -- there were 3 patients in DCCT. The patients in UKPDS, I don't think we have as much information. At least, we have the data from DCCT.

Early worsening really was -- along that

scale, there are various things that come on, and these lesions are like little micro hemorrhages, or microaneurysms, or those cotton wool spots. Quite often, they were white cotton wool spots that just disappear, and they went away, and they didn't get to be worse than the others.

That part of the scale is not vision-threatening, and there's a lot of flux back and forth, and there really wasn't any major change in terms of visual function for those patients in the end.

DR. LOW WANG: Thank you.

DR. WILSON: Dr. Yanovski?

DR. YANOVSKI: Yes. I have a question just regarding standard of care. If a patient is beginning intensification of insulin therapy, are there recommendations for more frequent ophthalmologic monitoring or just routine yearly eye exams?

DR. CHEW: That's a good question. I think we know that people who are in circumstances such as pregnancy, they are monitored much more

carefully. Our preferred practice pattern from the American Academy of Ophthalmology does say if they're going to be in rapid control, they should be monitored more frequently. We don't give a number or anything. Usually, it's based upon the baseline retinopathy, if it's mild, one year or so.

Really, we don't do a huge amount. If it's really a mild retinopathy, we don't expect a huge amount. I don't think it's malpractice not to see them not frequently because you expect it to happen, but nothing is going to really result in a disastrous vision loss in any way.

DR. WILSON: Peter Wilson. I have a question too. It's a two-part. The first is related to glucose, building a little bit on what Dr. Ferris was saying. The second is other risk factors.

The first part is, for glucose, is there a gradient? For instance, if a person starts with an A1c of 10 or 11 and has a first 2-year effect, do you expect more of a problem if they're starting high as opposed to starting lower with an

intensification of therapy, such as were seen in these trials? Have those analyses been done?

DR. CHEW: Yes, they've done that in DCCT, and they looked at -- every 1 percent decrease, it's a 35 percent reduction. If you're starting further up, you're going to more likely to have progression. That clearly is A1c-dependent.

DR. WILSON: Okay. So there is a gradient effect in a sense?

DR. CHEW: Yes.

DR. WILSON: The second part is what about non-glucose risk factors for eye disease? For a person who joins these trials, were there blood pressure effects? Maybe the blood pressure was also better controlled in the first 2 years. That must have been investigated. Is it really glucose that's the issue?

DR. FERRIS: One of the important messages in that early slide that Emily showed of the early worsening in the DCCT is the Y-axis, and the difference was like 1 and a half percent to 1 percent.

DR. CHEW: 1 percent, right.

DR. FERRIS: We tried very hard to look for these risk factors, but when you have 10 or 15 people, it's pretty hard. The impression was that a lot of them seemed to have a big drop. The data monitoring committee at that time worked very hard to look for different factors. Glucose seemed to be the most important one.

The other thing that was critical for the DSMC and the DCCT was that, for the most part, as Emily said, these people start with fairly mild retinopathy. And although they get a 3-step change, they don't know anything has happened to them. Their fundus photo looks different, but as far as symptoms or anything, with the exception of two or three of them, they haven't had any change.

Then the final thing, of course when you look at people that got worse early, they get worse. That seems to be true everywhere I've ever looked in my life. Yes, these people did worse because they did worse. It wasn't like they got worse, and then they all got better.

I think a lot of us feel like that intense improvement in blood glucose actually sort of speeded up where they were going to get to anyway. If you look at the curve, it sort of flattens out. That may be one of the explanations, and believe me, there are at least a dozen others.

DR. WILSON: Any more questions for Dr. Chew? Yes, Dr. Chong?

DR. CHONG: I don't actually have a question for Dr. Chew, but I just wanted to clarify and correct my response for Dr. Hiatt earlier.

The language on worsening with initiation of insulin is in adverse reactions, not warnings, with the insulin labels.

DR. HIATT: Thank you.

DR. WILSON: All right. Well, thank you very much, Dr. Chew. If we have any further questions, we'll make another request before the midday, be sure we'll get them to you.

I'm sorry. Will Hiatt, you do have another.

DR. HIATT: Just on this topic, the question that resonates in my mind, is it simply a function

of lowering blood sugar by any means, or is it unique to a particular drug class that carries a risk unique to the pharmacology of that drug class? We can belabor that later, but what I'm hearing is it sounds like it's more glucose-mediated than drug class-mediated.

DR. WILSON: If I understand, is it insulin or could it be other molecules that lower glucose? Let's hear the formal presentation by the sponsor and then by the FDA. And then perhaps if it's a question that might be directed to Dr. Chew even before the midday, we'll see if she could weigh in on that.

Why don't we move forward for our applicant presentation? I have a prelude for this I need to read.

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

presentation.

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

Now, we will proceed with Novo Nordisk's presentations. Thank you.

Applicant Presentation - Stephanie DeChiaro

MS. DeCHIARO: Thank you. Mr. Chairman, members of the committee, FDA colleagues, good morning. My name is Stephanie DeChiaro, and I am

direct of regulatory affairs for Novo Nordisk.

We are here today to review semaglutide, our new once-weekly glucagon-like peptide-1, or GLP-1 receptor agonist, for the treatment of adult patients with type 2 diabetes.

Type 2 diabetes is a progressive, chronic, metabolic disease that is associated with many serious comorbidities. The underlying pathophysiology in type 2 diabetes results in abnormal glucose metabolism and hyperglycemia. Untreated hyperglycemia can cause long-term complications. As such, glycemic control is fundamental for the management of type 2 diabetes.

In addition to improving glycemic control, weight reduction and prevention of complications associated with type 2 diabetes are key elements to modern type 2 diabetes management as stated in the most recent treatment guidelines.

Unfortunately, despite the abundance of treatment options, many patients still are not reaching their A1c goals. And thus, they remain at risk for both long-term micro and macrovascular

complications, affecting the kidney, nerves, and eye, as well as significant cardiovascular disease.

Semaglutide was designed and clinically evaluated to address the need that still remains in type 2 diabetes treatment. Specifically, we wanted a treatment that produce greater efficacy in weight loss than what is current available in a convenient once-weekly dosing regimen with the potential to positively impact complications of type 2 diabetes, as well as to robustly establish cardiovascular safety, with a safety profile that is consistent with a class of GLP-1 receptor agonists.

Our clinical development program to support the efficacy and safety of semaglutide consisted of eight phase 3 trials and evaluated over 8,000 patients. This program is called the SUSTAIN program. Five of these trials are considered our key efficacy trials and evaluated semaglutide throughout the continuum of diabetes care from newly diagnosed patients to those with longstanding disease. We also conducted two trials, specifically in Japan, based on local requirements.

These data are included in our overall safety evaluation of semaglutide.

Lastly, SUSTAIN 6 was a large, randomized, multicentered, dedicated cardiovascular outcomes trials, or CVOT, in adults with type 2 diabetes at high risk for cardiovascular events.

People with diabetes are at a high risk for these events. As such, we used the three-component composite endpoint of major adverse cardiovascular events, or MACE, as our primary endpoint in this trial. Based on the results from our comprehensive clinical program, our proposed indication for semaglutide is for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

In order to help patients reach their maintenance dose, we used an escalation schedule as shown here. Dose escalation should begin at 0.25 milligrams once weekly. After 4 weeks, the dose should be increased to 0.5 milligrams. The dose may be increased to 1 milligram if clinically indicated after at least another 4 weeks. In the

clinical setting, the physician and patient will individualize both dose and dose escalation timing. Semaglutide is administered through easy-to-use, prefilled, multiuse pens.

Overall, semaglutide once-weekly fills an important medical need by providing superior and sustained A1c control and body weight loss compared to commonly used diabetes therapies with demonstrated cardiovascular safety.

The overall safety profile of semaglutide is consistent with the class of GLP-1 receptor agonists. However, we did see an imbalance in diabetic retinopathy complications in SUSTAIN 6, the cardiovascular OUTCOME trial. We will describe our hypothesis for this observation later in the presentation.

I'd now like to take you through the agenda for the rest of our presentation. Dr. Anders Hvelplund will briefly describe the design of semaglutide and the clinical development program. And then he'll provide a summary of efficacy and primary outcome data from the program.

Dr. Stephen Gough will review the safety data on semaglutide. He will be followed by Dr. Lloyd Aiello who will provide background information and his perspective on diabetic retinopathy. Dr. Gough will then present data related to retinal safety from the semaglutide program.

Dr. Richard Pratley will provide his clinical perspective on the need for improved therapies and how semaglutide will fit into the currently available treatment options for type 2 diabetes. Dr. Gough will then conclude with benefit-risk considerations.

In addition to Dr. Aiello and Dr. Pratley, Dr. Darren McGuire is also with us today to help answer questions. All experts or their institutions have been compensated for their time and travel. Thank you, and I will now turn the presentation over to Dr. Hvelplund.

Applicant Presentation - Anders Hvelplund

DR. HVELPLUND: Good morning. I'm Anders Hvelplund, senior director, medical and science for

Novo Nordisk. Before reviewing the efficacy data, I would like to provide some perspective on the development and mechanism of action of semaglutide.

GLP-1 and the GLP-1 receptors are physiologically important in glucose and appetite control. The semaglutide molecule was designed as a long-acting, selective agonist of the GLP-1 receptor. It's a subcutaneously administered peptide that has a 94 percent homology to human GLP-1, and as a result has a very low antigenicity risk.

The prolonged action of semaglutide has been achieved by two modifications of the molecule: the binding to albumin through the attachment of a modified di-acid and a spacer and a modification to be stable against DPP-4 degradation.

On the next slide, I'll show how these properties translate into a once-weekly profile with low variability. The pharmacokinetic properties of semaglutide were evaluated in a comprehensive clinical pharmacology program. As illustrated by the figure, the pharmacokinetic

profile during a dose interval at steady state is relatively flat with low fluctuations between trough and maximum concentration. On average, the maximum concentration is observed 1 to 3 days post-dose.

In addition, the trial show that semaglutide has a half-life of approximately one week. Steady-state exposure was achieved following 4 to 5 weeks of once-weekly administration and was similar between injection sites, and it increased proportionally with semaglutide dose. Altogether, these properties are compatible with once-weekly dosing.

The clinical effects of semaglutide were evaluated in a large phase 3 program, which showed that semaglutide produced superior durable improvements in glycemic control relative to placebo and all comparators evaluated. In addition, semaglutide produced weight loss that was both clinically meaningful and durable. Additionally, semaglutide was evaluated in patients at high risk of cardiovascular events in a

dedicated cardiovascular outcomes trial, and in this trial, we established cardiovascular safety.

Let me walk you through the data that supports semaglutide's superior impact on A1c and weight loss and the data generated to establish the cardiovascular safety of semaglutide.

Here is an overview of our clinical development program supporting the efficacy of semaglutide. For purposes of this presentation, I will focus on the key efficacy trials SUSTAIN 1 to 5. In these trials, we explored the continuum of type 2 diabetes care from monotherapy in drug-naïve patients on the left of the slide, to combination treatment with commonly used OADs in the center, to combination with basal insulin on the right.

I will then review results from our large two-year standalone cardiovascular OUTCOME trial, SUSTAIN 6, that further support long-term efficacy and safety of semaglutide. Let me review the trial design for each of the five key efficacy trials.

For each of the trials, the primary objective was to evaluate the effect of semaglutide

once-weekly on glycemic control. All were randomized, parallel group, multicentered, and multinational trials evaluating efficacy and safety of semaglutide in patients with type 2 diabetes, and all but one trial included both doses of semaglutide 0.5 milligram and 1 milligram.

SUSTAIN 1 was a 30-week, double-blind trial comparing semaglutide to placebo in drug-naïve adults.

SUSTAIN 2 was a 56-week, double-blind trial comparing semaglutide to recommended maximum dose of sitagliptin as add-on to metformin, TZD, or the combination of the two.

SUSTAIN 3 was a 56-week open-label, two-arm trial comparing semaglutide 1 milligram to the maximum dose of exenatide extended release as add-on to one or two OADs.

SUSTAIN 4 was a 30-week open-label trial comparing semaglutide to insulin glargine as add-on to metformin with or without sulfonylurea in insulin-naïve patients.

Lastly, SUSTAIN 5 was a 30-week double-blind

trial comparing semaglutide to placebo as add-on to basal insulin alone or basal insulin in combination with metformin.

To mitigate gastrointestinal side effects seen with GLP-1s, all semaglutide-treated patients followed a fixed-dose escalation regimen. The starting dose was 0.25 milligrams. The maintenance dose of 0.5 milligrams was reached after 4 doses or 4 weeks of 0.25 milligrams, and then patients reached the maintenance dose of 1 milligram after an additional 4 weeks on the 0.5 milligram dose.

Inclusion criteria were chosen to ensure consistency across trials and that the enrolled patient population represented the broad intended target population. Patients in all five trials were required to have an A1c between 7 and 10.5 percent.

Patients in SUSTAIN 1 were required to be in a diet and exercise program at least 30 days prior to screening. Patients in SUSTAIN 2 through 5 were required to have been on stable treatments specified for each trial for at least 90 days prior

to screening.

The trials excluded patients with preexisting conditions such as a history of pancreatitis, severely impaired renal function, known proliferative retinopathy or maculopathy requiring acute treatment, certain cardiovascular or cerebrovascular events, and conditions related to medullary thyroid carcinoma.

The primary endpoint in all five trials was changed from baseline to planned end of treatment in A1c. The confirmatory secondary endpoint was changed from baseline to end of treatment in body weight. The study-wise type 1 error was controlled by prespecifying a testing hierarchy, including A1c and body weight for both doses of semaglutide.

We also had a number of supportive secondary endpoints. I will highlight a few of them in this presentation, including the proportion of patients who reached treatment targets of A1c less than 7 percent and the proportion of patients who obtained a weight loss response of at least 5 percent at end-of-treatment.

The analysis population used for efficacy was randomized patients who had received at least one dose of trial medication. This is the full analysis set. The primary analysis was a mixed model for repeated measurements. We used two observation periods when analyzing patient data.

The primary analysis was prespecified to target the effect of semaglutide while avoiding any confounding from additional concomitant medications. As such, this analysis was based on the observation period in which patients were on treatment without rescue medication.

Supportive analyses were based on an in-trial observation period in which patient data were included regardless of treatment or rescue medication use. Approximately 2,500 patients were randomized to semaglutide in the five efficacy trials compared to 1500 in the comparator arms. Efforts were made to follow and collect data on all patients for the planned duration of trials, even if treatment was discontinued.

The proportions of patients completing the

trials were high across trials, ranging from 91 percent and up to 96 percent. Almost all patients were included in the full analysis set.

Premature treatment discontinuations were generally low and with an average rate of approximately 12 percent in all trials, except SUSTAIN 3 where approximately 20 percent discontinued treatment in both arms. The high proportion of patients discontinuing treatment in SUSTAIN 3 is due to a number of reasons, including more patients withdrawing consent, lost to follow-up, and violation of inclusion/exclusion criteria.

Importantly, the proportion of patients discontinuing treatment due to a gastrointestinal adverse event in SUSTAIN 3 was comparable to the other SUSTAIN trials. The proportion of patients initiating rescue medication was generally low with semaglutide than with comparators.

Baseline characteristics across the trials reflected the broad type 2 diabetes population included. Just under 50 percent of patients were

women. The mean age ranged from 54 to 59 years. A total of 118 patients 75 years or older were included in the five key efficacy trials. Most patients were white, and across all trials, the mean A1c level was around 8.2 percent.

Patients in SUSTAIN 1, the monotherapy trial, had the shortest mean disease duration of approximately 4 years compared to patients in SUSTAIN 5 on top of insulin who had the longest mean disease duration of approximately 13 years. The mean body weight ranged from 89 to 96 kilos, and mean BMI was around 33.

Turning now to the primary endpoint results, semaglutide led to superior A1c reduction in all five trials for both doses. Here, we show the change from baseline in A1c. Semaglutide 0.5 milligram is in light blue, 1 milligram is dark blue, and placebo is in gray. Both semaglutide doses were superior in lowering A1c compared to placebo.

Similar superiority was observed when comparing to a widely-used OAD, sitagliptin in

orange, as well as when comparing to the GLP-1 receptor agonist, exenatide extended release, in yellow. And semaglutide was also superior to the most commonly used basal insulin, glargine, in green, and was superior to placebo when added on top of basal insulin as shown in gray.

The effect appeared to be dose-dependent with a 1-milligram dose showing greater improvement in all efficacy parameters. With semaglutide 1 milligram, A1c was reduced by 1.5 to 1.8 percent points, and with semaglutide 0.5 milligram, A1c was reduced by 1.2 to 1.5 percent points.

Consistently across all trials, all sensitivity analyses supported the robustness of the conclusions drawn from the primary analysis showing significant and clinically relevant treatment differences.

As seen in our two trials that went out to 56 weeks, semaglutide 0.5 milligram and 1 milligram resulted in durable improvements in glycemic control as shown by a reduction in A1c, evident already after 4 weeks of treatment and reaching

nadir after 23 to 30 weeks.

When looking at the proportion of patients reaching A1c less than 7 percent, up to 4 out of every 5 patients treated with semaglutide 1 milligram achieved A1c below the ADA treatment target of 7 percent represented on the Y-axis.

Up to 74 percent of patients achieved a glycemic target on the 0.5 milligram dose and up to 79 percent of patients on the 1 milligram dose. This compared to up to 40 percent for active comparators and up to 25 percent for placebo.

Semaglutide led to superior and substantial weight reductions versus all comparators in all five key efficacy trials. Semaglutide 0.5 milligram dose reduced body weight up to 4.3 kilos. The 1-milligram dose produced greater weight loss up to 6.4 kilos, and both doses produced greater weight loss than comparators across all trials.

The weight loss was an added effect observed in these patients receiving standard type 2 diabetes treatment and no specific weight

counseling nor any restrictions to caloric intake. The weight loss data highlights semaglutide as an improved GLP-1 receptor agonist with an up to three-fold greater weight loss compared to another once-weekly GLP-1 receptor agonist, exenatide extended release, in the SUSTAIN 3 trial.

Current American Diabetes Association guidelines recommend modest weight loss for overweight patients with type 2 diabetes where a modest weight loss has been defined as a sustained 5 percent reduction of initial body weight. Five percent weight loss has been shown to improve glycemic control and to reduce the need for glucose-lowering medications. In fact, guidelines instruct that when choosing glucose-lowering medications for type 2 diabetes in patients that are overweight or obese, one should consider their effect on weight.

In our key efficacy trials, we see significant results when looking at the proportion of patients who lost at least 5 percent of weight with semaglutide. Up to 46 percent for

0.5 milligram and up to 66 percent of patients on semaglutide 1 milligram lost at least 5 percent body weight. Importantly, these reductions in weight were maintained after long-term treatment of up to 56 weeks.

Overall, across five key efficacy trials, semaglutide resulted in clinically relevant, superior, and durable reductions in A1c versus all comparators and in all treatment regimens. These results were consistently supported by numerous sensitivity analyses, and significantly more patients reached the ADA treatment target of an A1c less than 7 percent.

Semaglutide also had substantial effects with regard to body weight that were maintained long term. Reductions in body weight were superior for both doses of semaglutide, and significantly more patients with semaglutide achieved at least 5 percent weight loss.

Turning now to our cardiovascular and long-term safety trial, SUSTAIN 6, SUSTAIN 6 was a two-year, randomized, double-blind,

placebo-controlled, multicenter, multinational trial to evaluate cardiovascular risk and long-term safety and efficacy with semaglutide in patients with type 2 diabetes at high risk of cardiovascular risk.

3,297 patients were randomized 1 to 1 to 1 to 1 to treatment with semaglutide 0.5 milligram, semaglutide 1 milligram, or corresponding placebo doses. The trial duration was 2 years for all patients with a 5-week follow-up period.

The primary objective of SUSTAIN 6 was to demonstrate the cardiovascular safety of semaglutide. Specifically, SUSTAIN 6 was design to exclude an excess cardiovascular risk by demonstrating an upper bound of the 95 percent confidence interval below 1.8 with a reassuring point estimate in line with the preapproved requirement specified in the 2008 guidance.

Enrollment was stratified by two groups: patients with established cardiovascular disease or chronic kidney disease who were 50 years and older, and patients with only evidence of cardiovascular

risk factors who were 60 years and older.

The primary endpoint in SUSTAIN 6 was the time from randomization to the first occurrence of a major adverse cardiovascular event, or MACE. These were adjudicated endpoints evaluated by an independent, blinded adjudication committee based on predefined criteria. MACE was defined by three components: non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.

We also looked at a number of endpoints expected in a cardiovascular outcomes trial, including expanded MACE and a combined microvascular endpoint. This endpoint evaluated progression of microvascular disease or use of treatments for microvascular disease. It was composite endpoint of new or worsening nephropathy and diabetic retinopathy complications. We also looked at long-term efficacy by means of change from baseline to 2 years in A1c and body weight. Other relevant endpoints are shown in your briefing book.

The analysis for SUSTAIN 6 compared the two

pooled doses of semaglutide versus placebo. The primary analysis was a stratified Cox proportional hazard model and included all randomized patients based on in-trial data. Patients who did not have an event was censored at the in-trial end date. Non-inferiority was concluded if the two-sided upper bound of the 95 percent confidence interval was below 1.8 for the primary MACE endpoint.

Overall, the proportion of patients completing SUSTAIN 6 was high with an approximately 98 percent completion rate. Vital status at end of trial was known for 99.6 percent of patients corresponding to the vitals that has been unknown for only 13 patients, 6 patients on semaglutide and 7 patients on placebo. Both of these measures reflect that the trial was well-conducted and indicate that the results are both robust and reliable.

Overall, demographics and baseline characteristics were consistent across all four treatment groups, and on this and the following slides, we show data for semaglutide pooled and

placebo pooled. Approximately 40 percent of patients were female. The mean age in both groups were 65 years and was higher from the SUSTAIN 6 population compared to the other phase 3 trials. Ten percent of patients were at least 75 years old.

Most patients in each group were white. The mean baseline A1c of 8.7 percent was higher, and the mean diabetes duration of 14 years was longer in SUSTAIN 6 compared with the key efficacy trials. The BMI was 33, and 70 percent of patients in each group had impaired renal function.

Cardiovascular-related conditions at baseline were prevalent as expected in this enriched population and were equally distributed across treatments. Most patients had hypertension, and ischemic heart disease was present in more than half the patients. Around a third had prior MI and 15 percent had prior stroke.

Turning now to the primary endpoint. The result of the primary analysis for time to first MACE demonstrated a hazard ratio of 0.74 and an upper bound of the 95 percent confidence interval

of 0.95; thereby, semaglutide met its primary endpoint and was non-inferior to placebo.

The Kaplan-Meier estimate of the accumulative risk of MACE at 2 years was 6.2 percent with semaglutide and 8.4 percent with placebo corresponding to an absolute risk difference of 2.2 percent.

The primary analysis excluded the 1.8 upper confidence interval bound that we prespecified and also provided substantial evidence of cardiovascular safety with 254 events collected over 2 years.

Importantly, all three individual components of the MACE endpoint, cardiovascular death, non-fatal MI, and non-fatal stroke, were consistent with the composite endpoint supporting the safety conclusion.

In addition to the standard three-component MACE, we evaluated cardiovascular safety using an expanded MACE endpoint that also included revascularization, unstable angina, and hospitalization for heart failure.

Expanded MACE, which is highlighted, mirrors the results of the three-component MACE. The components of the expanded MACE are shown here, substantiating cardiovascular safety. We also analyzed all-cause death with and without non-fatal MI or non-fatal stroke with no effect observed on all-cause death.

Type 2 diabetes is associated with increased risk of microvascular complications such as nephropathy and retinopathy. Improved glycemic control has been associated with improvements in microvascular endpoints.

In SUSTAIN 6, a combined microvascular endpoint of new or worsening nephropathy and diabetic retinopathy complications was prespecified as a secondary endpoint. Shown here is the result of the composite endpoint of time to first microvascular complication with an estimated hazard ratio of 0.86.

Looking separately at the components of the composite microvascular endpoint, there was a clear difference in the results. The nephropathy part

showed a hazard ratio of 0.64 and an upper 95 percent confidence interval of 0.88. This was a composite endpoint of microalbuminuria, doubling of serum creatinine, continuous renal replacement therapy, and renal death. And the effect observed was driven only by a difference in microalbuminuria.

In contrast, the diabetic retinopathy complications endpoint showed a hazard ratio of 1.76 and a lower bound of the confidence interval of 1.11. This was a composite endpoint of diabetic retinopathy complications which will be described in more detail by Dr. Gough.

SUSTAIN 6 also gave us the opportunity to look at long-term efficacy. On this slide, you see the HbA1c on the Y-axis and the duration of the trial in weeks on the X-axis. From a baseline of 8.7 percent, there was a substantial drop in A1c early in the trial for both doses of semaglutide. And similar to the results seen in the key efficacy trials, the reductions in A1c in SUSTAIN 6 was durable throughout the course of the two-year trial

period.

Semaglutide also promoted long-term sustained weight loss over 2 years compared to placebo on background of standard-of-care. From a baseline weight of 92 kilos, we saw substantial weight loss in the initial 44 weeks, and this was sustained for the duration of the trial.

To summarize, in SUSTAIN 6, we excluded excess cardiovascular risk by establishing non-inferiority for a 1.8 non-inferiority margin. All three individual components of the MACE endpoints were consistent with the composite endpoint.

The components of the expanded MACE further support cardiovascular safety. In totality, the data provides substantial and reassuring evidence of cardiovascular safety. Semaglutide provided long-term reductions in A1c and weight loss up to 2 years in SUSTAIN 6.

Overall, these results are consistent with the findings from the five key efficacy trials and demonstrate semaglutide's superior and durable

reductions in A1c and weight.

Thank you, and I'll now turn the lectern to Dr. Gough.

Applicant Presentation - Stephen Gough

DR. GOUGH: Thank you, Dr. Hvelplund.

I'm Stephen Gough, senior principal clinical scientist at Novo Nordisk and practicing endocrinologist with a specialty in diabetes. I will now discuss the semaglutide safety profile that was found to be generally consistent with the known safety profile of other GLP-1 receptor agonists in patients with type 2 diabetes.

The safety assessment of semaglutide was based upon two data sets from the completed phase 3a clinical trial program. The first includes pooled data from seven trials, SUSTAIN 1 to 5 and our two Japanese trials. These trials were of 30- to 50-weeks' duration. I will refer to this as the phase 3a pool.

This pool assessed the safety of semaglutide across a broad population of patients with type 2 diabetes. Due to important differences in trial

design, data from SUSTAIN 6, the cardiovascular outcomes trial of two-years' duration, are presented separately. The total patient years of exposure was over 10,000 of which the CVOT accounted for approximately 60 percent.

Let's start by looking at the overall safety profile of the phase 3a pool. Shown here are the proportions of patients with adverse events, serious adverse events, and adverse events leading to premature treatment discontinuation.

The proportion of patients reporting at least 1 adverse event was higher with semaglutide than comparators, including placebo, and the incidence of serious adverse events was also slightly higher in the semaglutide groups. Discontinuations were low, but higher with semaglutide.

Shown here is a table of the most frequently reported adverse events. Upon review by system organ class, the higher proportions of adverse events seen with semaglutide were mainly driven by gastrointestinal disorders, including nausea and

diarrhea as shown in the top part of the table. In general, these reactions were mild or moderate in severity and of short duration.

An increase in lipase levels was also reported more frequently with semaglutide than with placebo and active comparators. Each of these adverse events is consistent with the GLP-1 receptor agonist class.

Let's now look at the serious adverse events. In the phase 3a pool, the proportion of patients with serious adverse events was low. Generally, these were slightly higher with semaglutide than with comparator, but there was no increased risk of serious side effects observed with semaglutide 1 milligram compared to 0.5 milligram. The serious adverse events were distributed across several MedDRA dictionary system organ classes in both semaglutide and the comparator groups.

Fewer than 10 percent of patients discontinued treatment early due to adverse events. Both semaglutide treatment arms had more patients

discontinue treatment due to adverse events than the comparators. Among the discontinuations, most were in relation to treatment initiation and dose escalation, and gastrointestinal adverse events were the main drivers of treatment discontinuation. The highest proportion of the gastrointestinal events was seen in the initial months, during the escalation period.

Consistent with the dose response observed for gastrointestinal adverse events, the proportion of patients who discontinued early was higher with semaglutide 1 milligram than with 0.5 milligram.

Let's now look at SUSTAIN 6, the cardiovascular outcomes trial, which was of longer duration in the trials in the phase 3a pool and which included a heavily comorbid patient population at increased cardiovascular risk.

While the proportion of patients with adverse events in SUSTAIN 6 was similar across treatments, serious adverse events were reported in a smaller number of patients in the two semaglutide treatment arms compared to placebo. More patients

reported adverse events leading to discontinuation with semaglutide and more with the semaglutide 1 milligram dose.

Let me elaborate on the types and incidents of adverse events seen in the CVOT. We observed a similar an adverse event profile in the CVOT as in the phase 3a pool. The adverse events occurring with the highest incidence were nausea, diarrhea, vomiting, increased lipase, constipation, and decreased appetite.

In these categories, the incidences were generally higher with semaglutide than with placebo. In general, the other adverse events listed occurred in similar proportions across treatments.

Moving now to serious adverse events, as shown previously, the proportion of patients with a serious adverse event was lower with semaglutide than with placebo. Here, I show the proportions for the most frequently-reported serious adverse events.

In line with the cardiovascular events that

were confirmed by the event adjudication committee, most of the cardiac disorders reported as serious adverse events had lower incidents with semaglutide than with placebo.

There were more adverse events leading to treatment discontinuation in the two-year CVOT than in the phase 3a pool. This is most likely the result of the longer duration of the CVOT and the inclusion of the more vulnerable population with high cardiovascular risk. Nausea, vomiting, and diarrhea were among the most frequently-reported adverse events leading to discontinuation.

Moving on to deaths that occurred in the clinical trial program, as shown on this slide, the number of deaths was balanced between semaglutide and comparators. In total, in the phase 3a pool, 15 patients died during the trials, including 9 randomized to semaglutide and 6 to comparators. The total number of deaths was higher in SUSTAIN 6 to CVOT compared to the 3a pool, again reflecting the preexisting comorbidities of patients enrolled in the trial and the longer duration of the trial.

There were no imbalances between the semaglutide and placebo treatment arms.

Across the clinical development program, the causes of deaths did not differ between treatment arms and were consistent with what is expected for the patient population enrolled in the clinical trials.

In addition, specific adverse events of special interest were evaluated. These were based on observations in the GLP-1 receptor agonist class, important safety parameters for type 2 diabetes, and the population being treated. An external independent event adjudication committee, or EAC, performed ongoing blinded validation of selected adverse events according to predefined diagnostic criteria.

The EAC adjudicated events included neoplasms, pancreatitis, cardiovascular events, thyroid disorders, and diabetic retinopathy complications which was a composite endpoint as mentioned by Dr. Hvelplund.

We observed no differences between

semaglutide and comparators or placebo for acute renal failure or immunogenicity. Similarly, there were no differences between treatment arms for thyroid disorders, including EAC confirmed thyroid neoplasms, which I will summarize in a moment, together with the other types of neoplasms as this is an area of importance for GLP-1 receptor agonists.

Small differences in the instance of gall bladder disorders occurred as previously reported with other GLP-1 receptor agonists. All of these data can be found in the briefing book.

Focusing, therefore, on areas most relevant to the benefit-risk discussion of semaglutide, I'll start with episodes of severe hypoglycemia. No episodes of severe hypoglycemia occurred in the phase 3a pool when semaglutide was used as monotherapy. Episodes of severe hypoglycemia were infrequent when semaglutide was added to other agents.

As with other GLP-1 receptor agonists, these episodes mainly occurred when semaglutide was used

with sulfonylurea or insulin. The proposed semaglutide label will advise physicians to consider a dose reduction of sulfonylurea or insulin when using semaglutide with these agents to reduce the risk of hypoglycemia.

Similarly, in the CVOT, the episodes of severe hypoglycemia were infrequent, and there were small numerical differences between semaglutide and placebo. As was seen in the phase 3a pool, the majority of severe hypoglycemia episodes occurred when semaglutide was used with sulfonylurea or insulin therapy. It's important to remember that these low rates of hypoglycemia were achieved in the context of A1c reductions that were significantly greater with semaglutide than placebo.

Moving on to EAC confirmed events, I'll start neoplasms. Looking at malignant neoplasms, we see that the confirmed events was spread over multiple organ systems with no apparent difference between semaglutide and the comparators in the 3a pool.

Turning now to the CVOT where more events were reported in the trial reflecting the two-year duration and an older and more comorbid population, as in the phase 3a pool, the malignant neoplasms was spread over multiple organ systems with no clustering and no apparent difference between semaglutide and comparator for different tissues of origin.

Recognizing pancreatitis is an important safety topic for incretin-based therapies. Let's turn to the proportion of patients with events of pancreatitis. Using the prespecified criteria, the incidence of pancreatitis was low and comparable across the phase 3a pool, and most of the events were mild.

In SUSTAIN 6, the number of patients with acute pancreatitis was comparable across treatment arms with 8 semaglutide-treated patients and 10 placebo-treated patients. In the CVOT, all events of acute pancreatitis were classified as mild, using the prespecified Atlanta criteria. The EAC confirmed pancreatitis events in both the phase 3a

pool and the CVOT occurred throughout the trials with no indication of a lead time.

Next, moving to cardiovascular safety, as you heard from Dr. Hvelplund, we established cardiovascular safety of semaglutide. We saw a 2 to 4 beat per minute increase in pulse rate but a decrease in systolic blood pressure. This increase in pulse rate is similar to that seen for other long-acting GLP-1 receptor agonists.

SUSTAIN 6 was designed to meet the FDA pre-approval cardiovascular safety requirements. It had a 90 percent power to demonstrate non-inferiority of the upper limit confidence boundary of 1.8, thus requiring 122 MACE.

To collect data on long-term safety, an additional requirement of the trial was that all patients be followed for 2 years. At the end of the trial, 254 patients experienced MACE. Based on these events, the point estimate for SUSTAIN 6 was 0.74 with an upper bound of 0.95. These results are consistent across cardiovascular endpoints and in subgroups.

Consistent with the MACE results, we saw no excess of cardiovascular adverse events with semaglutide versus comparators across the entire phase 3 program. In summary, the data provides substantial and reassuring evidence of cardiovascular safety.

The final area of special interest is diabetic retinopathy complications which we assessed in the SUSTAIN 6 cardiovascular outcomes trial. Before I present our data, Dr. Lloyd Aiello will provide some background information to provide context around diabetic retinopathy.

Applicant Presentation - Lloyd Aiello

DR. AIELLO: Good morning. Similar to what you heard presented by Dr. Emily Chew earlier this morning, I'm here to provide background on diabetic retinopathy and to help with the observations from the semaglutide clinical development program and the perspective.

I am professor of ophthalmology and vice chair in the Centers of Excellence in the Department of Ophthalmology at Harvard Medical

School and vice president of ophthalmology and director of the Beetham Eye Institute at Joslin Diabetes Center.

I've been internationally active in the design, implementation, and analyses of clinical trials in diabetic retinopathy for over 25 years and was the inaugural chair of the Diabetic Retinopathy Clinical Research Network, now the largest network for clinical trials in diabetic retinopathy and diabetic eye disease in the United States.

Let me start with an overview of diabetic retinopathy. Diabetic retinopathy is one of the most prevalent microvascular complications of diabetes. In fact, most people with diabetes eventually develop some retinopathy.

At the time, they are diagnosed with type 2 diabetes, approximately 20 percent of patients have retinopathy, and this incidence increases to more than a half after 15 or more years of the disease. In approximately one-quarter of people, advanced sight-threatening disease arises after 15 years.

Diabetic retinopathy is characterized by a spectrum of changes as illustrated in these retinal photographs. These changes progress over time from none, as shown in your left, to non-proliferative retinopathy in the middle panels, to sight-threatening stages called proliferative diabetic retinopathy and/or diabetic macular edema as shown on the right.

Visual loss from diabetic retinopathy generally occurs from the severe stages of the disease. Abnormal new vessels may grow in on the retina and may bleed. These conditions are called proliferative diabetic retinopathy and vitreous hemorrhage. They are shown on the left and are often treated with laser photocoagulation.

In addition, diseased retinal vessels may leak fluid into the retina causing retinal swelling, a condition called diabetic macular edema as shown in the right. This condition is often treated with either intravitreal injections or laser photocoagulation.

In the SUSTAIN 6 trial, it was these

therapies and related late-stage complications which are expected from the natural history of the disease that comprised the adjudicated retinal endpoints.

To accurately detect and monitor diabetic retinopathy severity and its complications, our rigorous standardized classification system has been established internationally. This system is based on specific retinal findings and key procedures, such as pupillary dilation, experienced eyecare provider evaluation, ETDRS or equivalent photography, and protocol visual acuity measurement. When assessed in this manner, severity is well-correlated with the risk of retinopathy progression and risk of visual loss.

In SUSTAIN 6, some complications of diabetic retinopathy were evaluated. However, standard methods for assessing progression and severity of retinopathy were not used. This limitation is important as we consider the SUSTAIN 6 findings.

Let me now discuss how we treat diabetic retinopathy. Both the pathology and the

interventional approaches for diabetic retinopathy are similar in type 1 and type 2 diabetes. For patients with complications of diabetic retinopathy, we now have remarkably effective, sight-saving therapies. These therapies include laser photocoagulation, intravitreal agents including VEGF inhibitors, and surgery.

Not only can we now reduce the risk of severe visual loss to less than 5 percent, but we can also partially or fully restore prior visual loss from diabetic retinopathy, and even cause retinopathy severity itself to improve. However, our most important treatment goal is to prevent the onset or progression of retinopathy, so the challenge is how to care for the eyes of patients with type 2 diabetes before severe complications occur.

A fundamentally important aspect of care is optimization of blood glucose. We know the risk of diabetic retinopathy is highly associated with the degree of glycemic control and that reduction of hyperglycemia can both delay the onset and slow the

progression of diabetic retinopathy. This is true for proliferative diabetic retinopathy, and diabetic macular edema, and for both type 1 and type 2 diabetes.

Data conclusively demonstrating this benefit are exemplified by the results of the Diabetes Control and Complications Trial, we refer to as the DCCT. The DCCT evaluated over 1,400 patients with type 1 diabetes. The patients received either conventional or intensive diabetes therapy to normalize A1c.

Showing here are those patients without retinopathy at baseline. The intensive therapy group with its lower mean A1c is presented in orange. By year 9, intensive therapy was associated with 76 percent reduction in risk of retinopathy onset as compared with the conventional therapy group shown in green. Please note that substantial benefit took several years to become evident.

Benefits of better glycemic control were seen for retinopathy progression, development of

severe retinopathy, and the need for laser treatment or ocular surgery in both the primary and secondary intervention cohorts.

The United Kingdom Prospective Diabetes Study, or UKPDS, showed similar benefits of intensive glycemic control in patients with type 2 diabetes. In this study, every 1 percent decrease in A1c level resulted in a 37 percent reduction in the risk of microvascular complications, underscoring the long-term benefit of better glycemic control in type 2 diabetes. As seen in the DCCT, a substantial benefit took several years to become evident.

You can see here the delay before substantial benefit occurred in the DCCT. In fact, initially, in the secondary intervention cohort, there was what is now known as the early worsening phenomenon.

Focusing on the area within the red circle, you see that the intensive therapy group with its lower A1c shown in orange was actually at a higher risk of retinopathy progression during the first

2 years as compared with the conventional therapy group. However, the eventual magnitude of benefit in the intensive therapy group, seen to the right of the graph, far exceeded the degree of detriment observed early in the study as seen to the left of the graph.

Intensive glycemic control improved long-term outcomes even in the specific drug subgroup of patients who experienced early worsening. Here are DCCT data on the progression of retinopathy for those patients who did have early worsening by 18 months, shown in the solid lines; and here are the data for those who did not have early worsening at 18 months, shown with dashed lines. Note that the horizontal axis is years of follow-up after month 18.

The progression rate was higher in the intensive therapy group with early worsening, the solid orange line, compared with the intensive glycemic control group without early worsening, represented by the dashed orange line. Note the magnitude of the difference after 8 years of

follow-up as shown by the arrow.

Now, let's compare the intensively-treated group with early worsening, the orange solid line, to the conventionally-treated group without early worsening shown here by the green dashed line. We see that those with intensive control and early worsening did substantially better than those without early worsening but who received on conveniently glycemic control. Please note the large difference after eight years of total follow-up is shown by the arrow to the right. Thus, intensive glycemic control, when performed safely, is generally more important for long-term retinal outcomes than the possible detriment from early worsening that may occur.

This early worsening phenomenon is well-appreciated in both type 1 and to an extent, in type 2 diabetes. Risk factors include advance retinopathy, diabetes of long duration, poor baseline glycemic control, or profound improvement in glycemic control. Indeed, as you'll see later, these are the same risk factors that were

associated with diabetic retinopathy complications in SUSTAIN 6.

Early retinopathy worsening has been observed with many interventions that significantly improved blood glucose control, including insulin use, other GLP-1 receptor agonist, after bariatric surgery, and after pancreas transplantation.

Shown here are the 2017 recommendations from the American Diabetes Association for ophthalmological evaluation of patients with diabetic. Most patients, those with no or mild retinal disease, should be evaluated approximately yearly. As the severity of retinopathy increases, so does the frequency of ophthalmologic monitoring. Additional guidance is provided for patients undergoing treatment intensification since improved glycemia is linked to early worsening. This currently applies primarily with insulin.

Specifically, when initiating insulin in patients with longstanding poor glycemic control and severe or worse retinopathy, ophthalmologic monitoring at 3-month intervals for 6 to 12 months

thereafter is appropriate.

In some situations, for example, in patients with retinopathy already at or approaching the high-risk stage, it may be prudent to delay the initiation of intensive glycemic treatment until ophthalmologic interventions can be completed. This is particularly relevant if hemoglobin A1c is high. These recommendations are pertinent to all patients with diabetic retinopathy who are undergoing significant improvement in glycemic control regardless of a therapeutic modality.

In summary, diabetic retinopathy is a near-universal complication of diabetes. Clinical practice guidelines exist, and accurate methods for evaluating retinopathy are widely available. We currently have highly effective interventions for treating complications of diabetic retinopathy and multiple studies conclusively demonstrate that better glycemic control is associated with reduced risk of retinopathy prevention and visual loss.

Overall, the risk of potential early worsening of retinopathy when intensifying diabetes

therapy are offset by the large long-term benefit of reduced retinal complications with improved glycemic control. And finally, the risk factors and complications of retinopathy are well-recognized, and the retinopathy complications discussed can be effectively monitored, managed, and treated by adhering to current clinical practice guidelines. Thank you.

Applicant Presentation - Stephen Gough

DR. GOUGH: Thank you, Dr. Aiello.

With that background in mind, I'd now like to review the retinal data from the SUSTAIN program. As a reminder, a composite of diabetic retinopathy complications was part of the prespecified microvascular endpoint in SUSTAIN 6. However, the hazard ratio for retinal microvascular complications was greater than 1. To help the panel better understand this observation, I'll describe the study methodology and some of the post-study evaluations that we conducted and the conclusions that we have reached.

We collected adverse events of diabetic

retinopathy as part of standard adverse event reporting in both the phase 3a pool and SUSTAIN 6. In addition, in SUSTAIN 6, possible events of vitreous hemorrhage, onset of diabetes-related blindness, and the need for photocoagulation, and the need for treatment with an intravitreal agent was sent to the EAC for adjudication. We collectively termed these specific events diabetic retinopathy complications to represent clinically meaningful events that would be reported in SUSTAIN 6.

Hindsight suggests that more rigorous ophthalmological methodology would have generated higher quality data. To be clear, for the prespecified microvascular endpoint, we did not assess retinopathy severity, nor the occurrence of new retinopathy. Rather, we collected and adjudicated adverse event reports related to diabetic retinopathy complications and procedures used to treat retinopathy complications.

In the phase 3a pool, we excluded from the trials patients with known proliferative

retinopathy or maculopathy requiring acute treatment. In contrast to many diabetes therapeutic trials, SUSTAIN 6 included patients with all stages of retinopathy, including advance retinopathy, high baseline A1c, and long duration of diabetes history with minimal exclusion criteria.

Moving on to the data for adverse events related to diabetic retinopathy, shown here are adverse events potentially related to diabetic retinopathy based on searched terms from the MedDRA dictionary. In the phase 3a pool, the proportions of patients with retinopathy adverse events were low, and similar in the semaglutide and comparator groups. No serious adverse events were reported.

In SUSTAIN 6, more retinopathy-related adverse events occurred than in the 3a pool. This likely reflects the longer trial duration and the inclusion of patients with retinopathy at trial entry. Using this broad definition of retinopathy events, the incidence was higher in the semaglutide groups compared to placebo.

Moving on to the subset of diabetic retinopathy complications, this Kaplan-Meier plot shows the time to first EAC confirmed diabetic retinopathy complication in SUSTAIN 6. The difference between semaglutide and placebo gave a hazard ratio of 1.76 with a lower bound of 1.11. The treatment difference appeared early and persisted throughout the trial.

In total, 79 patients developed diabetic retinopathy complications, including 50 patients on semaglutide and 29 on placebo. To better understand these observations, we looked to the baseline characteristics of patients who experienced a retinopathy complication event.

In keeping with known risk factors for the progression of diabetic retinopathy complications, the 79 patients who had EAC confirmed events of diabetic retinopathy complications, compared to the overall SUSTAIN 6 trial population, had a longer duration of diabetes, higher baseline A1c, and were more likely to be receiving insulin treatments at baseline, likely indicating more advanced diabetes.

They were also characterized by having preexisting diabetic retinopathy, proliferative retinopathy, and/or a history of treatment with laser therapy or intravitreal agents. These risk factors are identical to those previously describe by Dr. Aiello for early worsening or preexisting diabetic retinopathy.

Long-term glycemic control can prevent or delay the progression or onset of diabetic retinopathy. However, initial improvements in glycemic control, especially when the reductions are large, can be associated with an early worsening of preexisting diabetic retinopathy.

To determine whether this phenomenon contributed to the observations in SUSTAIN 6, we looked at the association between the early changes in glycemic control and the incidence of diabetic retinopathy complications.

We saw that the maximal A1c reduction of nearly 2 percent in SUSTAIN 6 occurred by week 16, indicated by the red line. We then looked to the association between this A1c change at this 16-week

timepoint and the development of retinal complications in patients with and without preexisting diabetic retinopathy.

Patients without preexisting diabetic retinopathy had a low incidence of EAC confirmed events, regardless of A1c reduction at 16 weeks in both treatment arms. This is illustrated by the incidence rate of first event on the Y-axis as a function of various degrees of A1c lowering along the X-axis.

Among patients with preexisting diabetic retinopathy, the incidence rate was higher than in the group without baseline retinopathy in both treatment arms. Further, the incidence rate trended higher with greater reductions of A1c at 16 weeks in both treatment arms. The incidence rate at first event was highest in patients whose A1c fell by more than 1.5 percent at 16 weeks.

The increased risk of diabetic retinopathy complications seen with semaglutide is explained by the fact that 236 patients in the semaglutide group achieved A1c reductions greater than 1.5 compared

with only 76 in the placebo group. These results are consistent with the glycemia-related early worsening phenomenon.

To summarize in SUSTAIN 6, diabetic retinopathy complications, as defined by prespecified criteria, occurred at higher incidence with semaglutide compared to placebo. Baseline factors associated with a higher risk included preexisting diabetic retinopathy and a longer duration of diabetes compared to the overall SUSTAIN 6 population. Larger A1c reductions early in the trial were also associated with a higher risk. These observations are consistent with early worsening but has been observed with other highly efficacious glucose-lowering therapies.

As semaglutide's glycemic efficacy was greater than even we expected in SUSTAIN 6, we did not anticipate this finding. Because we did observe early worsening, the proposed label for semaglutide will include language about diabetic retinopathy that parallels labeling for insulin. This will include reference to the well-established

guidelines and protocols for the management of patients at risk of early worsening as described by Dr. Aiello.

I would now like to invite Dr. Pratley to discuss the use of semaglutide by physicians like himself who routinely treat patients with type 2 diabetes.

Applicant Presentation - Richard Pratley

DR. PRATLEY: Thank you very much, Dr. Gough.

Good morning, everyone, Mr. Chairman, members of the panel. My name is Rich Pratley, and I'm pleased to be here to present my perspective on semaglutide for the treatment of type 2 diabetes.

For over 30 years, my career has focused on improving the lives of patients with diabetes through both clinical care and research. I believe that semaglutide is an exciting new therapy that will significantly advance diabetes care.

As we know, diabetes is one of the most common chronic diseases in the United States, affecting over 29 million people, roughly 9 percent

of our population. By the year 2030, over 56 million people will be affected by diabetes in this country alone. The vast majority, 90 to 95 percent of cases in adults, are people with type 2 diabetes.

Diabetes is an important disease because of the high risk of developing serious chronic complications including cardiovascular disease, as well as microvascular diseases such as retinopathy and nephropathy.

Now, we've made a lot of progress in the management of type 2 diabetes over the last two decades, in part because of the introduction of several new classes of medications. But we still face many treatment challenges.

The American Diabetes Association recommends an A1c target of 7 percent for most patients with diabetes. However, it's estimated that over 14 million people have an A1c above 7 percent and just over 3 million have an A1c above 10 percent. This illustrates that there is still a significant unmet need to improve glycemic control in many

patients, and this reflects what I see in clinic.

The other problem we deal with regularly in clinic is obesity. Most patients with diabetes struggle with weight issues. In fact, it's estimated that 16 million patients with diabetes can be classified as obese, and over 4 million are considered severely obese with a BMI above 40.

It's now well-established that even modest weight loss of as little as 5 percent can improve metabolic parameters and associated comorbidities. What we really need in practice are anti-hyperglycemic agents that also result in substantial weight loss.

Another issue with deal with regularly in clinic is cardiovascular disease. As the prevalence of diabetes has increased, so has the burden of cardiovascular disease in this population. This is true for coronary heart disease, other forms of heart disease, and stroke. We know that virtually all patients with type 2 diabetes are at increased risk of cardiovascular disease, so it's imperative that the diabetes

medications that we use have an established cardiovascular safety.

With these challenges in mind, it's important that we have therapies that allow us to individualize treatment based upon each patient-specific profile. What we need are new therapies that improve glycemia, getting more people to goal, that reduce weight, have a low risk of hypoglycemia, and have demonstrated cardiovascular safety.

We also seek medications that can be used in a broad patient population, including the elderly, people with renal or hepatic impairment, and those with underlying cardiovascular disease. Finally, we look for simple and convenient treatments because in general, these will be associated with improved adherence. The data that we've seen so far show that semaglutide meets these needs.

Importantly, semaglutide offers significant advantages over existing type 2 diabetes treatments. In head-to-head studies, compared to the DPP-4 CYP inhibitor sitagliptin; the GLP-1

receptor agonist, exenatide ER; and basal insulin, glargine, semaglutide was superior at lowering hemoglobin A1c, achieving an A1c target of less than 7 percent, and reducing body weight. The risk of hypoglycemia with semaglutide is low, similar to sitagliptin and exenatide, and lower than with insulin.

Lastly, once-weekly dosing is simple and convenient, and the dose can be individualized with the flexibility to administer 0.5 milligrams or to increase to 1 milligram, if needed. Semaglutide provides a great option for patients who are struggling because they are overweight and not able to achieve their A1c goals. I have a lot of patients like this in my clinic, and I've shown you that there are millions of Americans who are also in this category.

Now, we've just heard about diabetic retinopathy, and I'd like to provide my clinical perspective as well. As clinicians, we recognize that retinopathy is a common complication with diabetes. Diabetes remains the leading cause of

blindness in U.S. adults. Indeed, a major rationale for controlling glucose levels is to prevent the development and progression of retinopathy. An important part of the effort to prevent vision loss is to ensure that patients have an annual dilated fundus exam or more frequent eye care as needed. This is actually part of our measures of quality in clinical practice.

Most providers are aware of the importance of screening for diabetic retinopathy, and they're also familiar with the phenomenon of early retinopathy worsening. The results of the SUSTAIN 6 trial remind all of us how critically important it is to follow the clinical guidelines in relationship to glycemic control and management of retinopathy. In doing so, we can help prevent vision loss in our patients with diabetes.

In summary, semaglutide is more than just another addition to the GLP-1 receptor agonist class. I really believe it presents the next generation of GLP-1 receptor agonists, and it advances our approach to treating type 2 diabetes.

Semaglutide offers clinically significant, relevant benefits with respect to glucose-lowering and weight reduction over existing treatments. And as a once-weekly injection, semaglutide will, in my opinion, improve adherence to diabetes management.

Moreover, the cardiovascular safety of semaglutide has been demonstrated in patients with high CV risk, those with renal impairment, and the elderly. As we've seen in the SUSTAIN 6 trial, semaglutide was actually associated with a reduction in CV events.

Overall, semaglutide allows us to broaden our approach to treating diabetes from one that is glucose-centric, to one that is patient-centered, comprehensive and focused on improving long-term outcomes. Thank you very much.

Applicant Presentation - Stephen Gough

DR. GOUGH: I will now conclude with the benefit-risk analysis for semaglutide based on all the key data summarized in the presentations.

With respect to benefit, once-weekly semaglutide produced superior and durable

reductions in A1c and body weight across five key efficacy trials when contrasted with all other comparators. Up to 79 percent of patients of semaglutide achieved target A1c values less than 7 percent. The reductions in A1c were durable in the five efficacy trials and in the two-year CVOT, and glycemic efficacy was supported across numerous sensitivity analyses and across subpopulations.

Semaglutide produced similar benefits with weight loss. Mean body weight loss was clinically meaningful and significantly greater than any of the comparators. Importantly, high proportions of patients on semaglutide achieved and maintained body weight reductions of equal to or greater than 5 percent than comparators in all of the trials. Additionally, SUSTAIN 6 established cardiovascular safety with semaglutide on top of standard of care in a long-term placebo-controlled cardiovascular outcomes trial.

The cardiovascular safety of semaglutide was demonstrated through non-inferiority analyses of time to first three-component MACE. Moreover, all

three individual components of the MACE endpoint were consistent with the composite endpoint. Taken together, these benefits from blood glucose, weight, and cardiovascular safety outweigh potentially risks.

Overall, the safety profile of semaglutide was consistent with that of other GLP-1 receptor agonists. The higher adverse event rate with semaglutide was driven by gastrointestinal events, which were mostly mild or moderate and of short duration.

The incidence of diabetic retinopathy complications in SUSTAIN 6 was higher compared to placebo. However, the absolute risk was low. We identified baseline factors that predict patients of the highest risk for diabetic retinopathy complications. Moreover, the observations were consistent with the known phenomenon of glycemia-related early worsening that is described in current insulin labeling. As you've heard from Dr. Aiello, current treatment guidelines include measures to monitor and manage this phenomenon.

The rates of pancreatitis and malignant neoplasms were low and similar between treatments, and we established cardiovascular safety. Finally, when looking at subpopulations, we have similar results for efficacy and safety in the elderly, renal impairment patients, and heart failure patients.

In conclusion, the data from the semaglutide clinical development program demonstrate a favorable benefit-risk profile in patients with type 2 diabetes. The data demonstrate that semaglutide is a significantly improved treatment option for patients with type 2 diabetes, including those at high risk of cardiovascular events. Semaglutide produced superior and durable glycemic control and weight loss and demonstrated cardiovascular safety in a once-weekly injection. The overall safety profile is also consistent with the well-established GLP-1 receptor agonist safety profile.

Thank you, and I'm now happy to answer any of your questions.

Clarifying Questions to Applicant

DR. WILSON: Thank you very much.

We're now going to move to questions for the sponsor, and clarifying questions as well. Please state your name for the record before you speak, and if you can, please direct questions to a specific speaker.

DR. HIATT: William Hiatt. I have two questions. The first is on the phase 3 trials that looked at A1c as the primary endpoint, and you used an analysis called mixed model for repeated measures, which I understand takes all available data and assumes that missing data are missing at random.

When you look through your material and try to understand the degree of missingness, it's a little hard to tell. If you look at how many patients were lost to follow-up at the end of those trials, there weren't a lot. I'm assuming most of the missingness occurred that there were specific timepoints when A1c values were simply not available in a particular study visit.

Is that assumption correct? And if so, I just wonder how much missing data there was that was used in your model because I know this will come up later and that would be challenged a bit, that that might overestimate the benefit of the A1c reduction.

So my first question is using a mixed model, how much missing data was there throughout the studies?

DR. GOUGH: Thank you. To take that question, I'll call upon our biostatistician, Lars Damgaard.

MR. DAMGAARD: Lars Damgaard, biostatistics from Novo Nordisk. It is correct that in our primary analysis as prespecified, we used subjects in a full analysis set and data that were collected by subjects who were on treatment and prior to initiating any rescue medication.

For your question in terms of missing data in that model, there were about 15 to 20 percent on the semaglutide treatment arms. As my medical colleague explained, we also collected data after

subject discontinued treatment and have completed follow-up on the patient. In that analysis that we call the in-trial analysis, meaning that we used data that are collected also after the initiation of rescue medication, we have missing data in the range from 5 to 8 percent.

If I may go on, for the question of whether or not the missing and random assumption is valid or not, I cannot tell. But the fact that we had complete follow-up on the subject, that allowed us to do compressive analysis of the data. And overall, we have a very consistent result, as you'll also see when we compare our result to the FDA briefing book.

DR. HIATT: Just so I understand this, if a patient is coming for a particular follow-up and they have an A1c value from the prior visit and one at the subsequent visit, then the missing value may be for a particular intermediate visit versus a patient who withdraws consent for which all their data becomes missing at that point in time.

MR. DAMGAARD: For your last point, if the

subjects are withdrawing consent, then we'll not have any more data.

DR. HIATT: Right.

MR. DAMGAARD: Yes.

DR. HIATT: But most of the missed -- the 20 percent seems like a large number to me, and that's missing in patients who have, at other time points, data that are available for analysis; is that correct?

MR. DAMGAARD: In the mixed model for repeated measurement, which was our primary analysis, that intermediate data was used to inform the analysis and the result that we have shown here today.

DR. HIATT: Was the missingness greater or less in the comparator arm compared to the study drug arm?

MR. DAMGAARD: Due to that, we actually censored data when subjects were initiating rescue medication. And we saw in the placebo trials in the comparator arm, up to 20 percent use of rescue medication, the missing data was larger in the

comparator arms, up to 30 percent.

DR. HIATT: Okay. I have a follow-on question, if I could, and that's a strategy behind the cardiovascular OUTCOME trial. The 2008 guidance has two thresholds, 1.8 and 1.3. My understanding at the time that was developed was that there wasn't a lot of MACE data available. It mainly came from adverse event reporting.

The 1.8 was a way to get on the market, but there was a subsequent requirement to cross 1.3, and that the 1.8 would be achieved because you could pool data from a number of your metabolic studies, phase 2, phase 3. And because it was early days in this request, it would be hard to get a lot of cardiovascular events, so 1.8 was a way to get on the market and 1.3 was to stay on the market, if I remember correctly.

In your design, your primary endpoint was to be less than 1.8, which I didn't see -- in your briefing document, the 1.8 is sort of the pre hoc, and 1.3 is the post hoc approach to this when the FDA is mainly 1.8. So I'm just a little confused

because if you're going to do a cardiovascular outcome trial, why not just prespecify 1.3 because you got to go there anyway? And maybe that's because you initially designed to acquire at 122 primary MACE events, which is not very many, and maybe that's why you went for 1.8. But then you went to 254 MACE events, so that's twice that.

So I'm just wondering about the strategy here. This is clearly a safety study, not an efficacy trial. You weren't looking for superiority. That's never been discussed here, which seems appropriate to me. But explain to me why it was 1.8 when in fact you clearly blew past that, and why it wasn't just 1.3 from the beginning and how you went from 122 to 254 events.

DR. GOUGH: You're correct that SUSTAIN 6 was designed as a cardiovascular safety study. To take you through the questions that you've posed though, I will call upon Anders Hvelplund to take you through exactly that.

DR. HVELPLUND: As you correctly state, the SUSTAIN 6 trial was designed to rule out 1.8, and

we only expected to accrue 122 events. We did the trial in order to ensure we had enough events in that we did not expect many events in our other phase 3 trials. That was the reason for doing the trial. We then planned to use the events also subsequently together with a post-approval trial to accrue a sufficient number of events to establish cardiovascular safety.

We did though in this trial because it was also prespecified to run for 2 years for all subjects, accrue more events than we expected, so we have now accrued 254 events. We did not prespecify the 1.3 analysis, but we believe now we have done the analysis post hoc with a very low p-value demonstrating that we have a lot of evidence for establishing cardiovascular safety in this population. But you are right that that was not prespecified.

DR. HIATT: I did read that the design allowed for both an event-driven and a time-driven study. When you went past 122 primary events, did you need to have a protocol amendment to approve to

gather more events because you let the trial run longer?

DR. HVELPLUND: No. The trial, as it was specified, had to accrue at least 122 events and be at least 2 years. In this instance, the 2 years was the deciding factor, so there was not a protocol amendment to gather more events.

DR. HIATT: And there was not an ethical issue for patients consenting to 122 events to go to 254?

DR. HVELPLUND: That was not how we specified the informed consent, no.

DR. HIATT: My last clarification, had you really stayed at 122 events and crossed 1.8, presumably you'd be required to do another outcome trial to get less than 1.3, correct?

DR. HVELPLUND: Yes.

DR. HIATT: Thanks.

DR. WILSON: Thanks very much. Next, Dr. Everett had a question.

DR. EVERETT: Thank you. This is really directed to Dr. Aiello because I have some

questions about the different endpoints for retinopathy. In particular, we talked a lot about early worsening with intensive glucose reduction, and we've sort of drawn an equivalence, or at least the presenters have drawn an equivalence, between the changes of three points on the ETDRS scale seen in the DCCT, and compared that or made an equivalence with the clinical events that occurred in the SUSTAIN 6 trial.

I'm not an ophthalmologist, but if I were to have diabetes, I would think that getting intravitreal injection would matter more to me clinically than having a change in the scale that I can't necessarily appreciate.

What I'm asking for is your sense as a clinician, as an ophthalmologist, as to how equivalent these two endpoints are and whether what we're seeing therefore in SUSTAIN 6 is actually a more severe change in the retinopathy than what would just be observed with a three-point change on a scale.

I can also have that question go to Dr. Chew

maybe later to see what her impression is, but I'd like to hear your response first.

DR. GOUGH: Thank you. To respond to that question, I'll call up Dr. Aiello.

DR. AIELLO: Lloyd Aiello, Harvard Medical School. You are correct, but they are related. When we look at retinopathy, we grade retinopathy along a spectrum from no evident clinical changes through the most severe sort of changes. Then we can look at how many steps are along that course. That, we commonly refer to as 1, 2, or 3-step worsening that you've heard about, and the way this study was conducted, that information cannot be obtained from the information.

What was obtained were either the end-stage type of complications or treatments for those end-stage complications, of which there were four, and which are expected with late-term complications. Now, what you need to recall within that is that as you get to a higher stage of the disease, you'll do 1, 2, 3-step progression. You will progress to that stage where it's severe, and

you can have these complications.

So it is well-established that a progression of those steps up in a higher stage will get you in places where you need treatment and that the treatment then can be very effective.

When you look at the complications that were looked at, they were the need for photocoagulation, which means that they were at a proliferative stage. Many of those are at a proliferative stage when they entered the trial.

Intravitreal injection, which can be used uncommonly for PDR but also very commonly now for macular edema, again, many of them in the SUSTAIN 6 trial were at the severe stage where they even had macular edema before coming in and they could be treated. Vitreous hemorrhage is a common complication of proliferative diabetic retinopathy and would be associated with that end of the scale.

It's a really a spectrum, and the key in the treatment is to try to prevent that progression, but if that occurs, to have them in ophthalmic care because we can treat those situations aggressively.

DR. EVERETT: If I can have a follow-up, maybe I'm stuck in the framework of a cardiologist where I think of surrogate endpoints and clinically relevant endpoints where we have, for example, LDL reduction being an endpoint analogous to change in a retinopathy scale, and then you have heart attacks, which might be more relevant for a vitreous hemorrhage, for example.

I guess my concern is that what we see in DCCT is something analogous to a change in a scale that's important and has a relationship with the outcome of interest, blindness or something similar in the long term, but maybe isn't that actual outcome. In this study, we have endpoints that are the actual outcome of interest, so I want to hear what you think about that potential analogy and that framework.

DR. AIELLO: In early studies where we didn't have our good treatments, we saw in the initial ETDRS studies and so forth was to look at an intervention for prevention of vision loss. The problem we have now, we have very effective

treatments.

The risk of vision loss from proliferative retinopathy is less than 5 percent, not per year, less than 5 percent in total. So it's almost essentially impossible to do a trial like that where you're going to try to look at a change in vision outcome for that. It is pretty well accepted, and even been accepted in concept from a regulatory agency and so forth, that the onset of the progression of these advanced diseases are clinically meaningful and clinically relevant because they would generally buy you an injection or buy you a laser, and the risk for vision loss.

DR. WILSON: Thank you. Dr. Brittain?

DR. BRITTAIN: My first question is have you made any attempt to get longer-term follow-up on the cohort, the CVOT cohort, to see if you see the crossing over of the event rates?

DR. GOUGH: No, we don't have them; that's bad information. The trial duration was specified by Dr. Hvelplund, and that's the latest point we have in terms of data collection. What I can tell

you is that within the diabetic retinopathy complications, you will remember there was a subset of patients who were reported as having diabetes-related blindness.

I have gone back to look at those after the time at which they had that endpoint specified or determined by the EAC, and what I can tell you is that we had information available on 3 out of those 5 patients. And in all three of those, the visual acuity had improved, and they no longer satisfied those criteria.

Importantly, the agency has also looked at those criteria and come to a different conclusion in terms of how many fell into that category. They identified one having diabetes-related blindness on semaglutide and one on placebo. Again, I can confirm that that one case, confirmed by the agency, also had an improvement in visual acuity, and we have no evidence of permanent visual loss.

DR. BRITTAIN: But would it be possible to go back to this same cohort and see how they are doing at this point?

DR. GOUGH: No, that would not be possible.

DR. BRITTAIN: I have a question, and I guess maybe it relates to my being confused about what this early worsening definition is. On slide CO-83, obviously, I must be misunderstanding something because I didn't understand why if someone -- so if someone has early worsening, they wouldn't necessarily have an event in this figure? Because normally, once you've had an event, you can't continue to have more events, so I don't understand -- I have a fundamental misunderstanding of the figure.

DR. GOUGH: To specifically address that question, I'll ask Dr. Aiello to come back, as he presented these data to you.

DR. AIELLO: I appreciate this is a difficult figure. It also is one I think that's critically important for this. If I can actually see CO-82, the slide before this.

Just to put it in perspective, this is the DCCT cohort, the conventional group in green, the intensive one in orange. You see here, as we

pointed out, the early worsening is quite clear in the first 2 years.

Now, the question that the next slide is answering is how did those patients who had early worsening do afterwards? In fact, I think it was raised earlier in our discussion to day. That's shown on the next slide.

So what's done here is at the 18-month time point, it was determined whether or not the patient, regardless of what group they were in, had early worsening or did not have early worsening, and they were going to see how those do over time in the study. And the green group here is a conventional treatment group, and the orange group here is the intensive treated group.

If you look just at the small arrow there, to the right between the orange groups, that shows that if you did have early worsening initially, you do do a little bit worse than if you didn't, compared to someone else who was also intensively controlled. But when you look now at the larger arrow, that's the comparison between those that had

improvement in glycemic control and early worsening compared to those that had no early worsening but had the regular control and didn't get the improvement early on.

You can see that the ones that had intensive control, the lowering of the A1c, even though they had early worsening, do much better than the other group. And this is part of the reason why we feel that in most cases, getting a person under intensive glycemic control earlier is better even though they might have early worsening.

DR. HIATT: Can I just clarify on that particular slide though? The groups are randomized to conventional versus intensive, but early worsening or no early worsening is a post-randomization event, therefore, it's confounding.

DR. AIELLO: It's a post-randomized observation in a mass manner prior to 18 months.

DR. HIATT: Yes. But now, you're comparing two different groups that have an event occurring after randomization. They can't be exactly

compared that way. I see your point.

DR. AIELLO: Correct. I'm not aware of any better way to look at them, nor am I aware of any other publication that can look at it in a more patient-centric manner over time in a study.

DR. WILSON: Dr. Neaton?

DR. NEATON: Maybe while Dr. Aiello is up there, I have a question on slide 89. But going back to the question that Dr. Everett raised, and there was a little bit of discussion recently, is it reasonable to speculate -- because you're looking at progression events here that are pretty severe, and you're not looking at the 17-point ETDRS scale.

Had one looked at progression as was done in these earlier studies on the ETDRS scale for a 2 or 3-point change, one would predict, I would guess, you would have a much greater incidence of progression than was observed in the study.

DR. GOUGH: Obviously, we weren't able to that analysis because we didn't do the ETDRS, but I will call upon Dr. Aiello to give a comment on

that.

DR. AIELLO: Theoretically, you are correct. We would expect to see progression rates in the short term higher in the group on semaglutide than the other group in the short term. Unfortunately, we can't look at that because, as was presented, the data were not evaluated in that way, but that would be the expectation.

DR. NEATON: I'm just responding to, I guess, the answer I heard that even though the -- this is a quote, "surrogate" in some people's opinion, including mine, that the 2 or 3-point change is considered clinically relevant by a lot of people and probably would not include, for many people, the kind of events we're talking about here.

DR. GOUGH: I think Dr. Aiello would agree with that, yes.

DR. NEATON: My question is on this slide, a couple of questions. One is, these four events, were they actually specifically targeted items at each exam that you checked off or were these

investigator-reported SAEs that you eventually have to go back and kind of determine from the SAE database?

DR. GOUGH: That's correct that these were collected through adverse event reports. When patients came for a hospital visit, they were collected as an adverse event. And if they were suspected of satisfying one of these criteria, further information was collected so that the EAC could make that --

DR. NEATON: Basically, the investigator had to determine that something met a serious adverse event, and they reported it, it was coded, and you went back and classified them in this way?

DR. GOUGH: It did not have to be a serious adverse event. It could have been any adverse event --

DR. NEATON: Any adverse event.

DR. GOUGH: -- related to diabetic retinopathy. And indeed, to make sure that we didn't miss any of these events, we then went on to do a comprehensive MedDRA search so when the EAC

actually looked at these potential events, they didn't just get events that came from the investigator. They were also asked to look at events that might not have been referred by the investigator but that we could pick up through adverse event reporting.

DR. NEATON: I think it's maybe a couple slides forward, 91. So in both the 3a pool and in the cardiovascular study, the way events were identified were similar, using the SAE database. The difference was that in the cardiovascular study, they went through an adjudication. But on this slide where there's no adjudication, it's comparable summaries in terms of how you define the events.

DR. GOUGH: Yes. As I say, the events that we referred to the DRC or went for adjudication did not have to be serious adverse events. They could have been any adverse event.

An important further difference, just to highlight between the 3a pool and SUSTAIN 6, which I'm sure explains why we have picked -- or one of

the explanations as to why we picked up more events is that in SUSTAIN 6, patients had an eye examination at 1 year and at 2 years. And I can show you that actually, this was the time at which those events were picked up, not necessarily through the eye examination but actually because they had an examination, and their eye's retinal status would have been discussed.

If I show you here --

DR. NEATON: Well, I was actually more -- I mean that would be interesting, but it just seems that your 3a pool, where patients were followed from 30 to 56 weeks as I understood -- I don't know what the time -- maybe you have data on the time course of these events, but that would be relevant, at least, in a crude way, to early ophthalmological problems --

DR. GOUGH: So --

DR. NEATON: -- associated with glycemic control.

DR. GOUGH: Yes. I do know the timing of events that certainly occurred in the early period

in SUSTAIN 6. I don't have specific details in relation to SUSTAIN 1 to 5. But in SUSTAIN 6 where we had the eye examinations, what this is showing is that the events that we picked up were then -- so these events could be used for referral or were used for a referral to the EAC.

You can see that most of the events were actually picked up at 1 year when they came for an eye examination, and then the second highest was at the end of trial. I think what it's telling us is something that we discussed earlier, is that many of these events were actually silent. If you don't look for these events, if you don't ask about them, you won't get them.

In SUSTAIN 6, we actually looked, we asked, and we detected them. This is quite different to other cardiovascular outcome trials in diabetes therapies, including of the GLP-1 receptor agonists, where there hasn't been this extra assessment. And therefore, it's likely that may of the adverse events have not been picked up, or might not have been picked up in other trials, but

we certainly picked them up in this trial by doing this examination.

DR. NEATON: Thank you.

DR. WILSON: Thank you. We're going to take a break. This is going to be a 15-minute break. We'll be back at 10:50, then we're going to have a presentation by the FDA. We have a list of others who want to ask questions, and we'll have a chance, following the FDA, to come back to the sponsor for these questions.

(Whereupon, at 10:37 a.m., a recess was taken.)

DR. WILSON: All right. If you all take your seats, please. We're going to get going, try to keep on schedule. Our next presentations are going to come from the FDA. Andreea Lungu? Thank you.

FDA Presentation - Andreea Lungu

DR. LUNGU: Good morning. I'm a clinical reviewer in the Division of Metabolism and Endocrine Products with the FDA. Today we will be discussing the safety and efficacy of the new

molecular entity, semaglutide. Please note that the updated slides have been printed and added to the AC package.

An outline of what we will cover is shown here. We will begin with a brief overview of the semaglutide and the clinical development program. This will be followed by a presentation of efficacy findings from the phase 3 trials. After this, we will turn to safety findings.

I will first present the general safety findings from the semaglutide clinical program. Dr. Hsueh will then present the statistical findings from SUSTAIN 6 for cardiovascular risk and diabetic retinopathy complications. After Dr. Hsueh's presentation, I will provide some additional discussion of the finding for diabetic retinopathy complications before summarizing the FDA presentations.

Semaglutide is a once-weekly GLP-1 receptor agonist developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Two therapeutic doses of

semaglutide are proposed: 0.5 milligram once weekly and 1 milligram once weekly.

Semaglutide would be the seventh member of the GLP-1 receptor agonist class. The currently approved drug products from this class are shown here. Dosing for the currently approved products ranges from twice daily to once weekly.

The phase 3 clinical development program for semaglutide included eight clinical trials. Five were multinational trials conducted to support the improved glycemic control indication. One was a cardiovascular outcomes trial of semaglutide versus local standard of care designed to exclude a relative risk of 1.8 for major adverse cardiovascular events. The remaining two trials were conducted in Japan, and they were mainly safety trials.

The five trials supporting the proposed indication are shown here. SUSTAIN 6 was a cardiovascular outcomes trial, and it will be presented in more detail by Dr. Hsueh during her presentation. The two Japanese trials were active

control on a background of oral anti-diabetic drugs.

Both dose strengths of semaglutide were studied in all but one of the phase 3 trials. In the trial comparing semaglutide to exenatide extended release, only the 1-milligram dose was studied. A titration scheme was followed to minimize gastrointestinal adverse events. All patients received a dose of 0.25 milligrams of semaglutide for 4 weeks. The dose was then increased to 0.5 milligrams. After an additional 4 weeks, the dose was further increased to 1 milligram for the patients randomized to receive 1 milligram of semaglutide. This was the same approach to dosing proposed by the applicant.

Having briefly covered the phase 3 clinical development program, I want to discuss the efficacy findings. The primary endpoint of the five efficacy trials was changed from baseline in hemoglobin A1c. Among the secondary endpoints, only change from baseline in body weight was included in the formal testing strategy.

For the statistical analysis, the full analysis set was used. This included all randomized patients that received at least one dose of study drug. The applicant prespecified an MMRM analysis using the on-treatment data. The MMRM method assumes that subjects with missing data behave similarly to subjects who do not have missing data. This assumption may not be appropriate as missing data tends to be associated with changes in treatment adherence.

The FDA's preferred analysis use multiple imputations of missing data based on the three dropouts. With each treatment arm, the missing data from subjects who did not adhere to treatment was imputed by the data from subjects who also did not adhere to treatment but had the measurement for the primary endpoint. The results that I will be presenting are based on the FDA's preferred method.

In the placebo-controlled trials, both doses of semaglutide resulted is statistically significant greater reduction in hemoglobin A1c at week 30. The treatment difference from placebo

ranging from minus 1.23 to minus 1.74 percent is shown here. Similarly, semaglutide resulted in a statistically significant greater reduction when compared to the active comparators that were studied.

Although not designed as a glycemic efficacy trial, the difference in hemoglobin A1c of 0.66 percent and 1.05 percent with semaglutide 0.5 milligram and 1 milligram respectively was seen in SUSTAIN 6 compared to placebo at the end of study.

As the study was designed to compare semaglutide versus placebo in combination with standard of care, an early difference in A1c might be reasonable. But this difference is expected to attenuate as patients on placebo start additional glucose-lowering therapies. Treatment with semaglutide also led to a statistically significant greater reduction in body weight. The body weight change difference from comparator, ranging from minus 2.4 to minus 5.6 kilograms.

I want to now turn to a discussion of the

general safety findings for semaglutide. The safety assessment was conducted using two main populations. The first was a pool of phase 3 trials that did not include SUSTAIN 6. Within this pool, additional subsets such as non-incretin and non-GLP-1 RA pool were considered when appropriate as some adverse events are more common with incretin therapies or specifically with GLP-1 receptor agonists.

The second population was patients from the cardiovascular outcomes trial. The number of patients in each pool is shown on this slide. Deaths and serious adverse events were generally balanced in both of the safety pools. The proportion of patients with events is shown on the slide.

Semaglutide-treated patients were approximately twice as likely to discontinue the study drug due to an adverse event. This was primarily due to gastrointestinal adverse events, and it appears to be dose-dependent.

Gastrointestinal adverse events are the most

common adverse events with GLP-1 receptor agonists. In the semaglutide program, gastrointestinal adverse events were identified based on review of the MedDRA-coded adverse events. Since GI events are known to be common with GLP-1 receptor agonists, the findings for the non-GLP-1 RA subsets of the phase 3 pool will be presented.

As shown here, treatment with semaglutide resulted in a greater incidence of gastrointestinal adverse events, serious gastrointestinal adverse events, and GI events leading to treatment discontinuation. The most commonly reported events were nausea, diarrhea, vomiting, and constipation, all of which were more common with semaglutide. Review of the data from SUSTAIN 6 presented on this slide show similar results.

Hypoglycemia is a concern for all anti-diabetic therapies. Assessment of the risk of hypoglycemia was done using a definition, which included events of severe hypoglycemia and events of hypoglycemic symptoms with a glucose less than 56. Based on data from the phase 3 pool and

SUSTAIN 6, semaglutide appears to have a low inherent risk for hypoglycemia. In SUSTAIN 5, which studied semaglutide on a background of basal insulin, the addition of semaglutide to insulin appeared to increase the risk of hypoglycemia.

Pancreatitis has been a concern with drugs that work through the incretin system, such as the GLP-1 receptor agonist. Adverse events of pancreatitis were adjudicated in the semaglutide program. The potential for an increased risk of pancreatitis was also evaluated through review of the MedDRA coded adverse events.

There were few cases of confirmed pancreatitis in the phase 3 pool and SUSTAIN 6. No significant difference was seen between treatment groups, but it is notable that all the events from the comparator arm in the phase 3 pool came from patients treated with exenatide extended release. In the non-incretin subset of the phase 3 pool, only two events were confirmed, both with semaglutide 0.5 milligrams.

The review of the MedDRA coded events

yielded similar results. Again, it is worth noting that all of comparator cases from the phase 3 pool were treated with either exenatide extended release or sitagliptin. Only three events were identified in the non-incretin subset, two with semaglutide 0.5 milligrams and one with semaglutide 1 milligram.

In addition to pancreatitis adverse events, the relevant laboratory data was also reviewed. The non-incretin subset of the phase 3 pool was used in exploring the data for serum amylase and lipase. Mean serum amylase increased in semaglutide-treated patients while remaining relatively unchanged in the comparator arm. Similar findings were seen in SUSTAIN 6. Of note, the mean amylase levels did not exceed the upper limit of the reference range.

A similar trend was observed for lipase both in the phase 3 non-incretin subset and SUSTAIN 6. Mean lipase levels increased over the course of the trials with both semaglutide doses while remaining relatively unchanged with comparator. Although the

levels increased, the mean lipase levels remain below the upper limit of normal for all treatment groups.

A general link between incretin-based therapies and gall bladder-related AEs has been suggested, as gall bladder emptying appears to be slower with this class of drugs. Gall bladder events were evaluated based on MedDRA terms. In the phase 3 pool, gall bladder events were slightly more common with semaglutide. This difference was mainly due to the non-incretin subset where only one event occurred with comparators. In SUSTAIN 6, no apparent difference in gall bladder events was seen.

Thyroid neoplasms were analyzed because of the theoretical concern of C-cell hyperplasia with long-acting GLP-1 receptor agonists. Additionally, the nonclinical data for semaglutide showed an association between semaglutide and C-cell adenomas and carcinomas in rats and mice.

All suspected cases of thyroid disease requiring thyroidectomy and thyroid neoplasms were

prospectively adjudicated. There were only 4 adjudicated events of malignant thyroid neoplasms in the phase 3 pool and 3 in SUSTAIN 6.

No meaningful conclusions can be made based on these events. However, it is noted that one of the patients treated with semaglutide had histopathologic evidence of thyroid C-cell hyperplasia. This patient had thyroid abnormalities at baseline that make it unlikely that the case was as a result of the exposure to semaglutide.

Serum calcitonin was also measured centrally during the phase 3 trials. A value more than 20 nanogram per liter was considered to be a value of special interest. No notable changes in mean serum calcitonin was seen in any treatment arm in any safety pool. In the phase 3 pool, the incidence of marked outliers was similar between comparators and semaglutide. In SUSTAIN 6, a slight increase in the incidence of serum calcitonin greater than 50 or greater than 100 was seen with semaglutide, however, the number of

outliers is very small.

Non-thyroid neoplasms were also adjudicated. There were slightly more malignant neoplasms with semaglutide in the phase 3 pool. In SUSTAIN 6, there was no significant difference in the proportion of patients with a malignant neoplasm between the treatment groups.

The risk for pancreatic cancer has been a concern for incretin-related drugs. Nine events of pancreatic cancer where EAC confirmed in the entire program, 4 in the phase 3 pool, and 5 in SUSTAIN 6. There was no imbalance regarding pancreatic cancer in the semaglutide program, however, the number of events is too small for it to be conclusive.

The risk for acute kidney injury exists for the GLP-1 receptor agonists. The renal safety of semaglutide was evaluated in a number of ways. These included a search of the MedDRA coded adverse events for events of acute renal failure and nephropathy, an adjudicated nephropathy composite, and review of renal laboratory tests. The adjudicated nephropathy composite was only done in

SUSTAIN 6, and I will discuss it in more detail when I discuss that analysis.

Review of the MedDRA coded adverse events did not suggest the risk for either acute renal failure or nephropathy with semaglutide. In SUSTAIN 6, a composite endpoint of new or worsening nephropathy was defined. This endpoint consisted of new onset persistent macroalbuminuria, persistent doubling of serum creatinine with eGFR less than 45, need for continuous renal replacement, or death due to renal disease. Persistence was defined as a confirmatory measurement within 12 weeks. No minimum time was required between the two measurements.

Treatment with semaglutide resulted in a decreased incidence in this composite endpoint. This difference is due to a difference in the persistent macroalbuminuria component, and no difference was seen with any of the other components.

We also reviewed renal laboratory tests, and looking at measures of mean eGFR change over time,

treatment with semaglutide did not appear to result in meaningful differences in eGFR versus comparator. eGFR declined over time for all treatment groups and was not evaluated after treatment discontinuation. Note that the Y-axis scales are different between the two figures on the slide as the baseline eGFR was different between the two pools.

As a peptide product, immunogenicity and hypersensitivity reactions were a safety area of interest for semaglutide. The potential for immunogenic and hypersensitivity reactions was assessed by evaluating the incidence of anti-semaglutide antibodies and by review of the reported adverse events.

Anti-semaglutide antibodies were reported in approximately 2 percent of patients and antidrug antibody titers were low. The neutralizing activity of antibodies is unknown due to unknown assay specificity issues.

Additionally, MedDRA searches were performed for allergic reactions, injection site reactions,

and potential immune complex diseases. The MedDRA search for potential immune complex diseases was not found to be specific, and I won't discuss it further.

The incidence of allergic reactions with semaglutide was similar to that of comparator. More injection site reactions were seen with comparator than was seen with semaglutide in the phase 3 pool. The majority of the comparator events occurred in patients treated with exenatide extended release, which includes a warning for serious injection site reactions in the approved prescribing information.

The discussion of vital signs will focus on findings for blood pressure and heart rate. A small decrease in systolic blood pressure was seen in the semaglutide-treated patients compared to patients in the comparator arms in both phase 3 pool and SUSTAIN 6. No significant difference in diastolic blood pressure was seen between the treatment groups.

An increase in mean heart rate was seen with

semaglutide-treated patients. Comparator-treated patients have no obvious change in mean heart rate over time. Despite the increase in mean heart rate, arrhythmia adverse events were not more frequent with semaglutide.

Dr. Hsueh will now present the findings from SUSTAIN 6.

FDA Presentation - Ya-Hui Hsueh

DR. HSUEH: Good morning. I'm Ya-Hui Hsueh, statistical reviewer from the Office of Biostatistics. I'm going to present our findings from the statistical assessment of cardiovascular safety and the retinopathy safety of semaglutide in the SUSTAIN 6 trial.

In this presentation, I will be discussing the cardiovascular safety of semaglutide based on the prespecified cardiovascular analyses. I will also discuss the signal for retinopathy associated with semaglutide observed in the trial.

Here is the outline of my presentation. First, I will provide a brief description of the trial design. Then I will present a statistical

assessment for both the cardiovascular safety and the retinopathy safety. Lastly, I will summarize our findings.

Let's start with the design of the trial. The primary objective of the trial was to demonstrate the upper bound of the two-sided 95 percent confidence interval for the estimated hazard ratio of primary MACE associated with semaglutide relative to placebo less than 1.8.

The primary MACE endpoint was defined as the composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The study protocol includes a long list of secondary objectives in addition to some secondary cardiovascular endpoints. This presentation will only discuss the composite endpoint of diabetic retinopathy complications.

The SUSTAIN 6 trial was a multinational, randomized, double-blind, and placebo-controlled cardiovascular outcomes trial. Adult patients with type 2 diabetes meeting all enrollment criteria were randomly assign 1 to 1 to 1 to 1 to treatment

with 0.5 milligrams semaglutide, 1 milligram semaglutide, 0.5 milligram placebo, or 1 milligram placebo, as an add-on to their standard-of-care treatment. The treatment duration was MACE event-driven. The trial duration was 109 weeks per subject, including a treatment period of 104 weeks and post-treatment follow-up period of 5 weeks.

The trial disposition and the treatment exposure was similar between the two treatment arms. A total of 3,297 subjects were randomized, with 1,648 randomized to semaglutide and 1,649 randomized to placebo. Approximately 98 percent of randomized subjects completed the trial. The median follow-up time was 109.7 weeks. About 89 percent of the subjects had at least 2 years of follow-up. The median treatment exposure time was 104 weeks.

The baseline demographic and the clinical characteristics appeared balanced between the two treatment arms. The mean age at baseline was 65 years old. The majority of subjects were white. Approximately 35 percent of subjects were recruited

from U.S. sites. The average BMI was around 33, the average duration of diabetes was about 14 years, and the average baseline HbA1c was 8.7 percent. About 29 percent of subjects had a baseline diabetic retinopathy. Majority of them had either non-proliferative retinopathy or unknown type of retinopathy.

Next, I will go over the statistical assessment for the cardiovascular safety. The following cardiovascular endpoints were prespecified. The primary endpoint was the composite MACE endpoint. The secondary endpoints that are presented in this presentation were expanded cardiovascular outcomes, all-cause death, and a composite MACE endpoint on-treatment plus 42 days.

All events included in this endpoint were prospectively adjudicated. The analysis population included all randomized subjects and followed the intent-to-treat principle. All endpoints are presented at the two-sided 95 percent confidence interval.

The prespecified statistical analysis was time-to-first-event analysis. The analysis was based on Cox proportional hazards model with treatment as covariate and is stratified by the following three baseline variables: evidence of cardiovascular disease, insulin treatment, and renal impairment status.

This table shows the results of primary analysis of MACE. A total of 254 MACE events occurred during the trial, 108 events in the semaglutide arm, and 146 events in the placebo arm. The estimated hazard ratio of MACE associated with semaglutide relative to placebo was 0.74 with a 95 percent confidence interval from 0.58 to 0.95.

Based on this result, the upper bound of the 95 percent confidence interval for the hazard ratio successfully ruled out a hazard ratio of MACE greater than 1.8 associated with semaglutide. The results of the individual components of MACE and the composite MACE on-treatment plus 42 days were consistent with the result of the primary MACE analysis.

This is the Kaplan-Meier plot of MACE comparing the two arms, semaglutide in blue line and placebo in green dashed line. The X-axis is time to event in weeks up to 112 weeks. The Y-axis is the estimated percentage of MACE with a scale ranging from zero percent to 12 percent. The two curves show how the events accumulate over time. The accumulative probability of MACE appeared to be higher in the placebo arm over time.

The results of secondary analysis of cardiovascular endpoints were consistent with the results of the primary MACE. A total of 112 all-cause death occurred during the trial, 62 deaths in the semaglutide arm and 60 in the placebo arm. The estimated hazard ratio was 1.05 with an associated 95 percent confidence interval from 0.74 to 1.5.

This forest plot summarizes the results of subgroup analysis of the primary MACE based on estimated hazard ratios. The risk of MACE associated with semaglutide was evaluated within subgroups defined by gender, age, race, and a

country of randomization. The point estimates were all less than 1. The data showed consistently lower risk associated with semaglutide across all subgroups on the risk of MACE.

Now, I will move on to the statistical assessment for the retinopathy safety. I will first discuss the prespecified analysis.

The prespecified endpoint of diabetic retinopathy complications was defined as the composite of need for retinal photocoagulation, vitreous hemorrhage, need for treatment with intravitreal agents, and diabetes-related blindness. All events were prospectively adjudicated. The analysis population included all randomized subjects.

The prespecified time-to-first-event analysis was based on the same stratified Cox proportional hazard model as the primary MACE analysis.

This slide describes how the retinopathy assessment was done in this trial. Retinal examinations were performed at baseline, year 1 and

year 2. Exam was performed by the investigator, a local ophthalmologist, or an optometrist according to a local practice. It was not recorded who performed it, and the dilation was not a requirement.

Results of the examinations were interpreted locally by the investigator and categorized as normal; abnormal, non-clinically significant; or abnormal, clinically significant. Evaluation of visual acuity was not part of baseline assessment, and no other eye examinations were scheduled as part of the protocol, but patients could attend visits with their own ophthalmologist as needed or scheduled.

Before I go to the results slides, please keep in mind that the following discussion is based on events as defined and adjudicated by the applicant. As noted in the FDA background package, there are concerns with the definitions used to identify events and with the results for some of the adjudications, particularly with respect to the events of blindness.

A total of 205 events were sent for adjudication. The event adjudication committee identified 98 events of diabetic retinopathy complications in 79 subjects. Note that each event could contain more than one component of the composite endpoint.

This table shows the result of the prespecified analysis of the composite endpoint and its four individual components. A total of 79 subjects experienced the composite event during the trial, 50 subjects in the semaglutide arm and 29 subjects in the placebo arm. The estimated hazard ratio of semaglutide relative to placebo was 1.76 with an associated 95 percent confidence interval from 1.11 to 2.78. This analysis showed an increased risk of diabetic retinopathy complications associated with semaglutide.

The Kaplan-Meier plot of diabetic retinopathy complications comparing the two arms is shown in this slide, the semaglutide arm in blue line and the placebo arm in green dashed line. The X-axis is the time to event in weeks up to

112 weeks. The Y-axis is the estimate percentage of diabetic retinopathy complications with the scale ranging from 0 percent to 5 percent.

This plot shows the imbalance between the two arms appear from the beginning of the trial and continued throughout the trial. The high rate of events was observed in the semaglutide arm during the early part of the trial. The cumulative probability of diabetic retinopathy complications appear to be higher in the semaglutide arm over time.

This forest plot summarizes the result of subgroup analysis of retinopathy based on estimated hazard ratios. The risk of diabetic retinopathy complications was evaluated within subgroups defined by gender, age, race, country of randomization, baseline HbA1c, baseline duration of diabetes, and baseline diabetic retinopathy. The point estimates were all greater than 1, showing consistently higher risk associated with semaglutide across all subgroups on the risk of diabetic retinopathy complications. The tests for

interaction between subgroups and treatment were not statistically significant.

This forest plot compares risk on a relative scale. One subgroup showed a noticeable difference on the absolute scale. Among patients with baseline diabetic retinopathy, semaglutide was associated with absolute risk increase of 3 percent, from 5.2 percent to 8.2 percent. However, in patients with no baseline diabetic retinopathy, the estimate absolute risk increase was just 0.3 percent, from 0.4 percent to 0.7 percent.

Even though the estimated relative risk was comparable by subgroup of baseline diabetic retinopathy, the absolute risk increase was very different, 3 percent versus 0.3 percent.

In the next few slides, I will discuss the details of the post hoc analysis and its limitations. The applicant conducted a post hoc analysis on the composite endpoint of diabetic retinopathy complications. The hypothesis of this analysis was that the increased risk of semaglutide

on diabetic retinopathy complications was mediated through the large initial rapid decline in blood glucose observed with semaglutide.

For this analysis, the change in HbA1c at week 16 was chosen as a marker for the initial rapid decline in blood glucose. Note that the change at week 16 was selected and made post hoc after the data was observed. The analysis in this section was based on Cox proportional hazard model that controls for baseline HbA1c, baseline diabetic retinopathy, baseline duration of diabetes, and the post-randomization change in HbA1c from baseline to week 16.

This table shows the results of the post hoc analyses. The estimated hazard ratio of diabetic retinopathy complications associated with semaglutide was 1.22 with an associated 95 percent confidence interval from 0.71 to 2.09. In the next two slides, I will further discuss the post hoc analysis using the causal diagrams that represent association between two or more variables.

The first diagram represents the

prespecified analysis of semaglutide on the risk of diabetic retinopathy complications as discussed in the previous section. It shows the total causal effect of semaglutide on diabetic retinopathy complications. The estimated hazard ratio of semaglutide relative to placebo was 1.76.

The second diagram represents the post hoc analysis of semaglutide on the risk of diabetic retinopathy complications. The sponsor argued that the total causal effect of semaglutide on diabetic retinopathy complications can be broken into two components: a direct effect of semaglutide that is not associated with a change in HbA1c at week 16 and an indirect effect that is mediated through the change in HbA1c at week 16.

The applicant argues that part of the total effect of semaglutide on diabetic retinopathy complications is an indirect effect of rapid decline in blood glucose, and that if you adjust for the indirect effect, the estimate direct effect of semaglutide on retinopathy, which is represented by the top blue arrow, corresponds to an estimate

hazard ratio of 1.22.

There are some limitations for the post hoc analysis. First, the estimated total effect is unchanged. Even if the causal model is correct, unless the indirect effect can be removed or reduced, the estimated total effect of semaglutide on diabetic retinopathy complications remains unchanged.

Second, the model might be incorrect. If the mediator model is misspecified, the estimate of direct and the indirect effect can be misleading.

Third, the multiplicity issue. Changing HbA1c at week 16 was chosen post hoc. It is unclear whether other variables in the other visit times were considered as possible mediators.

Here is the summary for causal relationship. From the data alone, we know that semaglutide is associated with both change in HbA1c and diabetic retinopathy complications. It is unclear which causal diagram best represents the relationship between semaglutide, change in HbA1c, and diabetic retinopathy complications. Even if the post hoc

model is correct, it is unclear how to remove or reduce the indirect effect between semaglutide, change in HbA1c, and diabetic retinopathy complications.

Finally, I would like to summarize our findings from the statistical assessment of semaglutide in SUSTAIN 6.

Here is the summary for the cardiovascular safety. The SUSTAIN 6 trial was designed to rule out a hazard ratio margin of 1.8. The estimated hazard ratio of MACE associated with semaglutide was 0.74 with an associated 95 percent confidence interval from 0.58 to 0.95.

The upper bound of the 95 percent confidence interval ruled out the risk margin of 1.8 in accordance with the 2008 FDA guidance. The results of the secondary analysis of cardiovascular endpoints were consistent with the result of the primary analysis.

Here is the summary for the retinopathy safety. The data showed an increased risk of diabetic retinopathy complications is associated

with semaglutide. Subjects with baseline diabetic retinopathy had an absolute risk increase of 3 percent associated with semaglutide. The absolute risk increase was small in subjects without baseline diabetic retinopathy.

Lastly, the sponsor's post hoc analysis has limitations, and it should be interpreted as hypothesis-generating. The causal relationship between semaglutide, change in HbA1c, and diabetic retinopathy complications cannot be clearly determined by this data alone.

Now, Dr. Lungu will further discuss diabetic retinopathy and to give an overall summary.

FDA Presentation - Andreea Lungu

DR. LUNGU: Thank you, Dr. Hsueh.

I want to now provide some additional comments on the findings of diabetic retinopathy. In addition to reviewing the analysis based on adjudicated events for diabetic retinopathy complications composite, the review of the reported adverse events was also performed.

In SUSTAIN 6, based on the reported adverse

events, an increase in risk for diabetic retinopathy events was seen with semaglutide compared to placebo. The most commonly reported term was diabetic retinopathy, though the terms retinopathy and vitreous hemorrhage were also more commonly reported with semaglutide compared to placebo.

In the phase 3 pool, review of adverse events did not identify any overall imbalance. Approximately, 2 percent of patients reported diabetic retinopathy adverse events. However, we should note the limitations with the data from this pool. The population enrolled in these trials was lower risk with only approximately 8 percent of patients being reported with diabetic retinopathy at baseline.

Additionally, there was no standardized follow-up retinal exam for most of the phase 3 trials. The two Japanese trials did have an additional follow-up retinal exam at the end of treatment. Of these two, one suggested an increased incidence of diabetic retinopathy events

with semaglutide, while the other did not show such a risk as shown in the table. We believe that this pool provides limited information for evaluating the risk of diabetic retinopathy with semaglutide.

We also consulted with FDA ophthalmologists for their expertise and for an opinion of the findings. The FDA ophthalmology consultant was asked to opine on the processes of in place to capture events, the adjudication, and significance of composite endpoint, and for an opinion on the significance of the finding.

With regard to the procedure in place to capture events, the FDA ophthalmologist did not believe them to be adequate. There was no standardized approach to evaluating the fundus. Exams could be dilated or undilated and could be performed by investigator or by a local ophthalmologist or optometrist. Additionally, no formal grading or scoring was used. Use of formal grading allows for better capture of retinal changes and captures multiple levels of progression.

The FDA consultant also had concerns with the components of the endpoint. One of the components was termed need for photocoagulation or intravitreal agent, however, there is no uniform agreement on what characteristics indicate a need for treatment.

Further, while it was termed need for treatment, positive adjudication of an event require that treatment had actually been administered, and many factors can influence whether or not photocoagulation or intravitreal injection is administered.

While vitreous hemorrhage may be a reasonable endpoint, the duration and severity was not captured, limiting assessment of clinically significant events. The component term, diabetic-related blindness, was also felt to be inadequate for the purposes of evaluating diabetic retinopathy as it could include events of loss of visual acuity not related to diabetic retinopathy, even including reversible events such as cataracts.

Lastly, while the definition of blindness

was appropriate in identifying legal blindness of any cause, it was not always followed in identifying patients with blindness in SUSTAIN 6. Even with the concerns with respect to the process and endpoints, the FDA ophthalmologist agreed that there was a signal for risk but concluded that the findings are consistent with what would be expected given the decrease in hemoglobin A1c.

The FDA ophthalmologist did not raise any ophthalmic concerns or believe that there was a need to restrict the patient population or alter the approach to dose titration. This was supported by the understanding that based on the findings from DCCT, long-term benefit in diabetic retinopathy complications may be expected with improved glycemic control despite an early retinopathy progression.

While better glycemic control has been shown to lead to better outcomes for retinopathy, we believe that there is some remaining uncertainty for semaglutide. In the Diabetes Control and Complications Trial, an increased risk for

progression of diabetic retinopathy in patients with type 1 diabetes and retinopathy at baseline was seen in the first 2 years in the group with better glycemic control. Starting at year 3, however, that group showed a reduced risk. There is no data beyond 2 years with semaglutide.

Similar findings of reduced risk for retinopathy have also been reported in large trials for patients with type 2 diabetes. The UKPDS and the ACCORD Eye Study both reported a reduced risk for microvascular complications such as retinopathy. An early increased risk was not reported in either of these, so that may be due to not performing repeat funduscopic exam in the early period. The UKPDS first evaluated retinopathy at 3 years, while the ACCORD Eye Study did so at 4 years.

The data from semaglutide fall somewhere between these trials. The data comes from patients with type 2 diabetes and show an early increased risk; however, the data limited to 2 years and the long-term outcome is unclear. It is unknown

whether the observed risk will go away and whether we will see a long-term benefit from improved glycemic control with semaglutide as we would expect based on previous trials. Also, reviewing what was seen with other cardiovascular outcomes trial may be relevant in considering the data from SUSTAIN 6.

In looking through what has been reported in previous cardiovascular outcomes trials reviewed by the FDA, we did not find a signal of increased risk. A small imbalance was seen with liraglutide, but this was not statistically significant. With empagliflozin, there was a suggestion of decreased risk, but again, this was not statistically significant.

However, it is important to note that the capture of events was different for each of these trials and that this limits the comparison. The difference in hemoglobin A1c between the active arm and placebo was around 0.4 percent for both of these trials.

I will now summarize the FDA's findings for

semaglutide. Semaglutide has been studied to improve glycemic control in five multinational clinical trials in a variety of patients from drug-naïve patients to patients on basal insulin. The mean change from baseline in hemoglobin A1c range from minus 1.3 to minus 1.7 percent at 30 weeks compared to placebo.

Semaglutide treatment also resulted in a statistically significant reduction in body weight with a mean change from baseline in body weight of minus 2.2 to minus 4.7 kilograms at 30 weeks compared to placebo.

The safety profile of semaglutide was generally consistent with other GLP-1 receptor agonists. The most common adverse events reported with semaglutide were gastrointestinal adverse events. Additionally, semaglutide appears to have a low inherent risk of hypoglycemia. Despite increases in amylase and lipase, no correlation with clinical events of pancreatitis was seen in the clinical program.

Gall bladder events were more common with

semaglutide in the non-incretin subset of the phase 3 pool, however, such a difference was not seen in SUSTAIN 6.

There does not appear to be any evidence for increased risk of C-cell tumors or other malignancies with semaglutide. Renal events were also not more common with semaglutide versus comparator.

SUSTAIN 6 was designed to rule out the hazard ratio of 1.8 for major adverse cardiovascular events. The Cox proportional hazard model estimated a hazard ratio of MACE associated with semaglutide of 0.74 with a 95 percent confidence interval of 0.58 to 0.95.

The upper bound of the 95 percent confidence interval ruled out the risk margin of 1.8 in accordance to the 2008 FDA guidance. An increase in heart rate as well a decrease in systolic blood pressure were seen with semaglutide.

An increase in diabetic retinopathy complications was associated with semaglutide treatment with a hazard ratio of 1.76 and the

95 percent confidence interval of 1.11 to 2.78.

Subgroup analysis did not show any significant interactions between various subgroups in treatment. Patients with diabetic retinopathy at baseline had a higher absolute risk increase associated with semaglutide treatment.

A post hoc mediator analysis controlling for the effect of treatment, in this case, A1c lowering in the first 16 weeks of treatment, yielded a lower hazard ratio of 1.22 with a 95 percent confidence interval of 0.71 to 2.09. However, there are limitations to this analysis. Even if the model is correct, the estimated total effect is unchanged.

Additionally, the modified change in hemoglobin A1c at week 16 was chosen post hoc rather than being prespecified. It is unclear whether other variables could be possible mediators.

Additionally, per the FDA ophthalmology consultant evaluation, assessment of retinopathy was not standardized and the definition of the endpoint was not adequate, further limiting our

interpretation of the results.

While acknowledging the retinopathy signal with semaglutide, the FDA consultant felt that the findings were consistent with the expectation given the decrease in hemoglobin A1c and that there was no need to restrict the patient population or alter the dosing. However, a similar risk of retinopathy was not seen with other antidiabetic drugs that had cardiovascular outcomes trial reviewed by the FDA, although assessment of retinopathy was different.

Additionally, the data on semaglutide is limited to 2 years, and it is unclear whether the risk of diabetic retinopathy will follow what was seen in previous studies where a benefit on retinopathy was seen beyond three years of intensive glucose control. With the available data, the long-term effect of semaglutide treatment on diabetic retinopathy is unknown.

This concludes the FDA presentation. Thank you.

Clarifying Questions to FDA

DR. WILSON: Thank you very much. Now, we

are open for questions for the FDA. Dr. Hiatt?

DR. HIATT: Thank you. William Hiatt. I'm just still pondering the design of the cardiovascular OUTCOME trial. A couple of key components, one is there's no interim analysis proposed, and two is that the initial sample size was based on a hazard ratio of 1, upper bound of 1.8. 122 events would, I think, clear that upper bound.

I'm assuming if the results showed a hazard ratio of 1.7, the FDA would have required another study; is that correct? Yes, that's correct, to get to 1.3?

DR. CHONG: I just want to clarify. You're saying the point estimate or the upper bound?

DR. HIATT: The upper bound. Under the original trial assumptions, they assume the hazard ratio of 1 and their hypothesis testing was non-inferiority with an upper bound of 1.8, had they had a result showing an upper bound of 1.7, they would have met their prespecified endpoint but they would have not met the second half of your

guidance, which says that you'd have to have an upper bound of less than 1.3 to continue marketing the drug.

Would you have required another cardiovascular outcome trial in that case?

DR. CHONG: That, in some part, would also depend on what the point estimate was. We'd have to be reassured that the point estimate wasn't a concern for cardiovascular risk.

DR. HIATT: Sure.

DR. CHONG: But if the situation were that the point estimate number was 1, hazard ratio of 1.7, I suspect we would likely require an additional study to exclude 1.3.

DR. HIATT: Okay. Here's my question based on those responses. With 122 events and no interim analysis, one wonders what the hazard ratio and upper bound would have been had you analyzed the first 122 events. Did anyone at the FDA consider doing that?

(No audible response.)

DR. HIATT: Why not? Because it makes you

wonder, doesn't it? Why go to 254?

Now, the out was, the design allowed for a certain amount of exposure. But it also, in my mind, would say if I went into this trial trying to rule out 1.8, I'd rather avoid a second outcome trial; I'd rather get my upper bound less than 1.3. Why not double the number of events and assure myself, I'm going to get less than 1.3?

DR. SMITH: I think you're getting to discussion question number 4.

(Laughter.)

DR. SMITH: Clearly, what you're describing and whether somebody analyze that event -- I don't know that they did -- any of those will be post hoc. As we listen to your discussion this afternoon, if that sounds like an exercise that we should take into our consideration of where things go from here, we'll listen and think about it.

We're going to be asking you to discuss what you think of the cardiovascular safety here. So I think we probably shouldn't get too off on what they could have done but rather focus on the data

before us.

DR. HIATT: Yes. I'm not asking the sponsor; I'm asking you. If you take the prespecified event-driven endpoint of 122 events, and they doubled that, did anyone at the FDA statistically decide to look at the first 122 events to have them to see what confidence intervals might have looked like at that point in time? It doesn't sound like anybody did that.

(No audible response.)

DR. HIATT: Did not, okay.

DR. HSUEH: No, we haven't done that.

DR. HIATT: That's interesting. Thank you very much.

DR. WILSON: All right. We have about 10 minutes before we're going to take a lunch break. A couple of things, any specific clarifying questions for FDA right now? And then either for the FDA or for the sponsor, anything where we would like them to do some clarifying work during lunch to provide, for instance, a back-up slide or something, let's frontload those issues now because

it gives them time rather than during our discussion period.

Dr. Palevsky, do you have such an item?

DR. PALEVSKY: I have one for the FDA. There was mention made after the sponsor's presentation that when you looked at the blindness events, that the attribution to retinopathy that was made was different than the five events attributed in the data presented; but that was not reflected in what was presented now.

Did I misunderstand the comment made earlier?

DR. CHONG: The data presented were based on just the events as adjudicated. The previous comment was accurate. Delving into the in-depth details of those events, it was unclear whether or not it was blindness-related retinopathy, reduced visual acuity that met legal blindness of other etiology. But we did not show that additional breakdown in our slides.

DR. PALEVSKY: It might be useful for us to see that information.

DR. LUNGU: If we can see slide 9.

DR. CHAMBERS: Wiley Chambers. I'm an ophthalmologist with the FDA. The issue is if somebody develops a cataract, you can't tell if it's from diabetes or if it is a normal aging process. There were also other inconsistencies with the reporting of individual patients, patients that are elderly that did not report to have cataracts or did not report to have things like presbyopia, which is directly age-related.

So it raised the question about how accurate that reporting was, and that was the source of the confusion on why those particular events were picked.

DR. WILSON: Dr. Ferris?

DR. FERRIS: I'm not sure how much I want to delve into this because I'm totally confused on the one hand and appalled on the other hand as to how we're looking at these changes in retinopathy. Maybe the sponsor can help clarify some things for me.

At some point, we see some numbers about the

proportion with proliferative diabetic retinopathy, but then I saw a slide that said they were categorized in an astounding categorization of diabetic retinopathy as normal; normal, not clinically significant; abnormal -- whatever the hell that is -- and then abnormal, clinically significant.

How that's different than abnormal, I can imagine, but there is classification scheme for diabetic retinopathy, which might have been more useful such as no diabetic retinopathy, microaneurysms only, moderate non-proliferative diabetic retinopathy, severe non-proliferative diabetic retinopathy, and proliferative retinopathy.

One of my questions is, how do they come to the conclusion that there were 20 percent with proliferative retinopathy? I may have misinterpreted the slide. That's a lot of proliferative diabetic retinopathy in a community. So I'm confused about that, appalled that the assessment could be undilated by an optometrist.

I'm nervous about retina surgeons on a dilated exam being reproducible. This, I just don't know what to make of it.

Then I'm confused by this baseline retinopathy of 8.2 versus 5.2 percent. What is that in this categorization? And if that is the baseline, then there's a 1.6 relative risk of more retinopathy in the treated group. And then I'd be interested in how the adverse experiences were verified.

In particular, I don't know whether these are patient-based outcomes, whether they're eye-based outcomes, whether a patient can have more than one outcome. A patient could get treated for proliferative retinopathy with photocoagulation, have a vitreous hemorrhage, which cause blindness, and have three events at once. So I don't know how they were added up.

DR. WILSON: Let's hold the response to that because that's almost a discussion item, so if we could get any clarifying information first; then I think in the discussion period after lunch from the

sponsor related to what the issues that Dr. Ferris brought up, and then perhaps any other additional information from FDA. But let's table that because that's going to go for a while. I believe that's part of our discussion.

Anything else before lunch, especially for clarifications? Yes, Dr. Li-Ng?

DR. LI-NG: I just had two questions actually. On the 79 events of the diabetic retinopathy complications, how many of those events occurred while the patient was on TZDs? And also, is there a breakdown of which ones were in the semaglutide 0.5-milligram group and which ones occurred in the 1-milligram group, and whether there was a difference?

DR. LUNGU: I don't know how many patients were on TZDs. I guess I could look, and I don't know if the applicant knows. But with regard to the doses of semaglutide, out of the 50 events on semaglutide, there were 25 and 25 even. There was no dose response.

DR. WILSON: Dr. Robotti?

MS. ROBOTTI: Thanks. Actually, I'm not a doctor, but thanks for the promotion.

(Laughter.)

MS. ROBOTTI: I'm a consumer rep. I am struck by slide number 17, the subgroup analysis of MACE, the U.S. versus non-US MACE events, particularly considering that 70 percent -- I think this is in study number 6 -- particularly since something like 70 percent of the participants were non-US.

It looks distinctly different to me. On the semaglutide group in the U.S., 7 percent had a MACE event and 7.9 percent on placebo did. But for non-US, it's 6.3 percent to 9.3 percent. That's close to a 50 percent increase in MACE events.

My concern is that wouldn't imply that those are not comparable groups, that there's a significant --

DR. WILSON: Excuse me. Dr. Robotti, what slide are you referring to?

MS. ROBOTTI: Seventeen.

DR. WILSON: FDA number 17.

MS. ROBOTTI: FDA number 17, subgroup analysis.

DR. BRITTAIN: I think it's the statistics sections.

MS. ROBOTTI: Oh, I'm sorry. I did not look up the statistics --

DR. BRITTAIN: Yes, it's in the statistics section, 17.

MS. ROBOTTI: Thank you, Dr. Brittain.

DR. BRITTAIN: Yes, that's what she's talking about.

MS. ROBOTTI: That's the one, bottom two lines, U.S. versus non-US. There's my concern. That looks significantly different to me, and I'm just wondering if that implies that they're not comparable groups, yet they're being merged for the purposes of analysis.

DR. HSUEH: They are comparable between the semaglutide and placebo. And between the U.S. and non-US, we don't have the analysis for that.

MS. ROBOTTI: So --

DR. HSUEH: In that case, it's comparable.

Yes, that should be --

MS. ROBOTTI: Shouldn't they be comparable --

DR. HSUEH: -- comparable, right.

MS. ROBOTTI: And they're not, are they?

DR. HSUEH: We did not look at between U.S. and non-US.

MS. ROBOTTI: Okay. And another question, a follow-up question, to that would be, where out of the U.S. were these trial participants? Are they comparable societies?

DR. HSUEH: Do you have want to make a comment?

DR. WILSON: FDA has some clarification on this.

DR. ANDRACA: Thank you. This is Eugenio Andraca, Office of Biostatistics. We also have looked at the characteristics of the patients within the U.S. and the non-US, so they could have different characteristics, different standard of care. Within each country, the rates could be different.

What we're looking here is comparisons controlling for U.S., controlling for non-US, comparing placebo to semaglutide. And in that respect, the relative risk was consistent in the sense that the interaction was not significant.

MS. ROBOTTI: Okay.

DR. WILSON: Dr. Robotti, is that adequate, or do you want further --

MS. ROBOTTI: I guess it's -- I just question the entire ethnic/racial profile of the participants overall, but I'll bring that up again during discussion.

DR. WILSON: Any other questions before lunch?

First of all, Dr. Neaton has been very patient. Do you have anything to say?

DR. NEATON: My question, I do have one for clarification, but it can wait until after lunch.

DR. WILSON: Any others before we break? Dr. Budnitz, go ahead.

DR. BUDNITZ: This is a question on the findings from other CVOTs, just comparing the

LEADER and the EMPA-REG trials. Did I hear correctly that the change in A1c for those trials is about 0.4; is that correct?

DR. LUNGU: Yes.

DR. BUDNITZ: And then for this trial, it was about 1?

DR. LUNGU: Yes.

DR. BUDNITZ: And were there any other comparison of similar baseline characteristics like MACE rates

DR. WILSON: Dr. Budnitz, what slide are you referring to?

DR. BUDNITZ: This is slide 10 in the section of further discussion of findings for diabetic retinopathy.

DR. LUNGU: I can look into baseline characteristics comparison. We actually didn't do that, but yes, there's a difference in A1c control over time. Also, those trials were a little longer, three to four years, and the events were captured differently.

DR. BUDNITZ: So I'm just thinking, we might

need a little bit more information to try to see if these other CVOTs are comparable in terms of risk for --

DR. LUNGU: I'll look at the population, and I'll let you know.

DR. WILSON: A couple more. Dr. Rosenberg? Yves Rosenberg?

DR. ROSENBERG: Thank you. Maybe you can check that data from the LEADER trial. The other 0.4, maybe that was at the end of trial but not overall. And there was also a big difference at the beginning.

But I do get your point into the comparison with the other trials and the fact that it didn't show that early increase, the point I wanted to make before you made a presentation. But I think that's going to be the heart event in our discussion.

Maybe the question I would ask for the FDA ophthalmologist is I'm a little confused about how they think the problem with the ascertainment and the choice of the eye endpoint would affect the

outcome. I can understand it would affect the precision of the result, but randomized trials such as this, how would that affect the relative risk? That's not clear to me.

DR. CHAMBERS: Wiley Chambers. If I can't trust the particular endpoints to be accurately recorded, it's potentially random noise. It may be randomized between the trial and it may be a finding, but if I can't trust whether it's a real event, I don't know how to necessarily interpret that.

DR. ROSENBERG: I understand. I agree to introduce noise, but unless you are convinced or some suspicions there's an outcome ascertainment bias, I don't see how that would affect the relative risk.

DR. CHAMBERS: I have no reason to believe that there is ascertainment bias.

DR. WILSON: Okay. Dr. Palevsky, you get the last question before lunch.

DR. PALEVSKY: As the token nephrologist in the room, it did not appear that there was any

signal related to renal outcomes. But the data provided don't have the degree of clarity that would be needed and included a lack of information on some of the baseline data, so if this could be provided.

New onset of persistent macroalbuminuria, assuming that's greater than 300 micrograms per milligram, need to know the data on baseline. Someone going from 298 to 302 is very different than someone going from 5 to 290, so having some data beyond that categorical endpoint.

Persistent doubling of serum creatinine NGFR less than 45 can only be interpreted with good data on what the baseline were. I didn't see baseline data provided, although in one of the figures, it looks like the baseline mean eGFR was about 75. But a little bit of data on that would also be reassuring.

Then there's a definitional issue, and this probably relates to something that the agency needs to deal with. Continuous renal replacement to a nephrologist means something that's happening in

the intensive care unit because that's a treatment that's being provided 24 hours a day.

I assume that what's meant by continuous renal replacement is chronic dialysis or transplantation, and the terminology that's used should be terminology that is not confusing. If we can just clarify that that's actually what was meant and moving forward use the correct words.

DR. WILSON: Okay. I stand corrected by Commander Bonner. In fact, the last question is going to come from Dr. Low Wang.

DR. LOW WANG: I do have a question about the stats section that was presented by the FDA. It's slide number 10. We've already talked about a lot of the problems of trying to figure out what the baseline level of retinopathy was for the patients. But in this table on the very bottom line, the non-proliferative retinopathy and the unknown are lumped together. I was wondering if we could break out the unknown. I was wondering what percentage of patients had an unknown retinopathy status at baseline.

DR. HSUEH: It's 9 percent for the unknown.

DR. WILSON: Unless there are any further questions, comments that need -- I think we have a few things that have been requested. One would be any ancillary ways of summarizing the eye findings with the recognition that this is not a standard approach that was used in this trial, and then also for Dr. Palevsky for renal and albuminuria. Those are the key elements, I think, and many of the other issues, we're going to be able to address during discussion, though.

We're going to back at 1 o'clock; 1 o'clock we'll reconvene, and we'll have an open public hearing with presentations.

(Whereupon, at 12:05 p.m., a lunch recess was taken.)

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

(1:02 p.m.)

Open Public Hearing

DR. WILSON: Good afternoon. We have some introductory remarks before our open public hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial 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 encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

With that said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair, and thanks for your cooperation.

We have -- what is it, 13 or 14 -- 13 speakers, so let's try to be efficient. For each

speaker, as we call your number, please go to the podium, introduce yourself, state your name any organization you are representing. And we'll start with -- go ahead, Commander Bonner, number 1, right?

CDR BONNER: Yes.

DR. BLONDE: My name is Larry Blonde. I'm an endocrinologist at the Oxford Medical Center in New Orleans, Louisiana, and I am here representing the American Association of Clinical Endocrinologists, the largest organization of clinical endocrinologists committed to enhancing the ability of members to provide the highest quality patient care, provides information and education about diabetes and other endocrine disorders, and publishes guidelines including those for diabetes and a comprehensive type 2 diabetes management algorithm.

The National Clinical Care Commission Act passed by Congress last week should help improve effectiveness of federal diabetes programs and was supported by the diabetes community and spearheaded

by AACE.

The burdens of type 2 diabetes have been well-discussed today. There are enormous, both personal and societal, costs associated with diabetes. Cardiovascular disease, the leading cause of death in people with type 2 diabetes, on the left, we see the years of life lost related to diabetes compared to peers, and on the right, we see the increased hazard ratio for mortality, both for cardiovascular death and all-cause mortality, related to diabetes.

This is data from a recently published New England Journal paper that pointed out that in Sweden between 1998 and 2014, mortality and the incidence of cardiovascular outcomes declined substantially among those with and without diabetes, although the outcomes associated with type 2 diabetes deaths were associated with less than controls.

While we can't cure diabetes controlling glucose levels and other cardiovascular disease, risk factors can greatly decrease complications,

but many patients don't achieve therapeutic targets. Among the many barriers are concerns about hypoglycemia and weight gain with some antihyperglycemic therapies if one looks at some of the consequences of hypoglycemic events of reduced well-being, productivity, and increased overall costs. And severe hypoglycemia can be associated with increased cardiovascular events and mortality.

In terms of weight, recent NHANES data from 2015 and 2016 show that 39.8 percent of adults and 18.5 percent of youth in this country are obese, and we've already heard about the issues with obesity and overweight in people with diabetes.

The AACE algorithm is designed to help clinicians better use therapies to achieve targets for glycemic control in people with diabetes and has always emphasized those treatments that have a lower risk for hypoglycemia or weight gain in their recommendations.

AACE does not advocate for the approval of any specific mediation, however, there's a great need for new antihyperglycemic medications to help

address the ever-increasing burden of type 2 diabetes. New, more effective medications associated with lower risk for hypoglycemia, possibly lower adverse cardiovascular disease events, and less weight gain or even better associated with weight loss can improve glycemic control and hopefully outcomes for people with type 2 diabetes.

Thank you very much for letting me address you today.

DR. WILSON: Thank you very much. Speaker number 2, please introduce yourself and go.

MS. VALENTINE: Hi. My name is Virginia Valentine. I'm an advanced practice nurse in Albuquerque, New Mexico. I practice at La Clinica De La Esperanza, and I'm also the medical director for Health-Scripts, a company that focuses on NPs and PAs. I'm representing myself. I've been a speaker for all the companies making GLP-1s since 2005.

Since the introduction of the GLP-1 receptor agonist class in 2005, we've seen excellent blood

glucose-lowering outcomes from these meds, but sadly, the uptake in healthcare professionals has been suboptimal, especially considering the value that they bring.

I think there are several reasons for this. First was the suspicion of pancreatitis and that whole brouhaha, which has turned out to be not nearly as dire as one would have predicted. Also, then the second is that payers have done their best to keep these clamped down because of the cost. But also, I think the payers had their suspicions that these might lead to weight loss -- their suspicions were true -- and they don't want to do anything to help the patients with weight loss if they can help it. They would rather just blame the patient for their failures.

Then thirdly, the primary care providers have not taken up this class of drugs, which is very sad. I think some of it is their concern about the time for training, although they use basal insulin. I think then you have to say, well, maybe they just really haven't understood the

value, and that's something I think that we have to work on a lot.

Semaglutide has now presented us a culmination of excellent A1c reductions, plus weight loss, which is a great combination, potentially cardiovascular risk reduction. But now the greatest benefit is the once-a-week dosing, which is a really important thing for patients.

I've always asked my patients, well, at least in recent years, would you rather have a once-a-day or a once-a-week? Ninety-five percent, I want once-a-week. It not only provides a lot of freedom and flexibility for patients but also for family members who have to be involved in helping patients.

I just wanted to point out that I think most patients can maintain this regimen, they can persist with this regimen, and I would ask that you all consider this next step in the GLP-1 story. Thank you.

DR. WILSON: Thank you. Speaker number 3, please introduce yourself.

DR. ARODA: Good afternoon. My name is Vanita Aroda, and I'm a physician investigator and endocrinologist at MedStar Health Research Institute, representing myself. For my disclosures, I have served as a clinical trials investigator or consultant with various companies involved in novel diabetes therapeutics, including Novo Nordisk. My travel to this meeting was paid for by the applicant. They have not had any input to my voluntary presentation.

I served as the principal investigator at MedStar Health on three studies evaluating semaglutide, and it is a privilege to share my firsthand experience on these studies in the context of my 15 years of experience of treating diabetes.

The two most common concerns I hear from patients with type 2 diabetes are one, "Why are my sugar still high? I'm taking the medicines my doctor prescribed, but they are still high." And secondly, "I cannot seem to lose the weight. I want to, but it's just not coming off."

These two basic questions in diabetes are writ with such a strong sense of guilt. I vividly remember one patient recently who said to me that her doctor said, "Just try harder. Just try harder." She was so angry with this response, she had brought in her diaries, her meter, her medications, and this is what her well-intentioned doctor said, "Just try harder."

When we as providers see the numbers of non-success, whether it be A1c or weight, we all want to understand why, aka, the differential diagnosis, yet this often ends up in diabetes, in conversations of guilt and a sense that we are not doing something right, we're not trying hard enough. Yet we, as clinicians, need to make sure we give the requisite tools so that when patients try, they succeed.

This is the story I have directly seen unfold with semaglutide as an investigator in the studies, that it helps patients, either early on or even after trying and failing with multiple other medications, to achieve glycemic control better

than what we have seen with previous agents, and in this process finally, finally battling that excess weight.

It is this dual success that translates to a sense of control and satisfaction for both the clinician and the patient. And as I have experienced firsthand in the studies, it has allowed the conversation to transform from one of a feeling of guilt and inadequacy to one of empowerment and self-advocacy, which is extremely rewarding.

I'm excited to see that we are now finally targeting, in a clinically meaningful pathophysiologic yet practical approach, both diabetes and weight control, both short and long-term outcomes with both the clinician and patient perspectives in mind. Thank you.

DR. WILSON: Thank you very much. Speaker number 4, please state your name and any organization you represent.

MR. BROWN: Good afternoon. My name is Christopher Wayne Brown. I'm from Selma, North

Carolina. In accordance with their company policy, Novo Nordisk has paid for my travel expenses to attend today's committee meeting.

In April of 2014, I was diagnosed with type 2 diabetes. I decided to seek out a new physician with a primary field of interest in diabetes management. I came under the care of Dr. Michael Soboeiro in June of 2014. He prescribed metformin and recommended the usual dietary restrictions and exercise, but I struggled with these lifestyle changes. As a result, my glucose levels did not improve.

In January of 2016, Dr. Soboeiro discussed with me the possibility of being a candidate for a clinical trial for semaglutide. I agreed and began the trial drug in February 2016. By the end of the clinical trial, I had lost 30 pounds, and my A1c was reduced from 8.1 to 5.4, all the while still struggling with the recommended diet restrictions and exercise.

During the trial, I remained on metformin, and after the study ended, continued on metformin

with the addition of daily injections of Victoza. Over the last 11 months, since the end of the trial, my A1c has slowly risen to a barely acceptable number, and I've regained 15 pounds.

In my case, the semaglutide was not only beneficial as can confirmed by my medical results but was more convenient since it was a weekly injection as opposed to daily.

Last week, Dr. Soboeiro called and asked if I would be willing to tell the members of this committee of my experience with semaglutide, and I'm very excited to have had this opportunity to come here today and tell you that my hope is that this drug will be approved for my doctor to prescribe to me and others living with this disease. Thank you.

DR. WILSON: Thank you very much. Speaker number 5, please approach the podium, state your name and any organization you represent.

MR. CONNOR: Good afternoon. My name is James Thomas Connor, and I reside in Irving, Texas. According to the company policy of Novo Nordisk,

they have paid my transportation and lodging to speak at this conference.

I am a retired CPA. I was in the profession for 44 years, and my job is stressful or was stressful and long hours. In 2001, I was diagnosed with type 2 diabetes. This was done by University of Texas Southwest Medical School's Ashton Clinic.

Initially, they scared the heck out of me, I can assure you, because I thought amputation and all these bad things. They put me on a diet with a dietician. I lost 60 pounds. I was on metformin, and I actually got off of metformin. For a couple of years, I didn't take it. But because of work and I was getting older, I basically had to get back on another drug called Actos.

I took Actos until a couple of years ago, and UT Southwest, as people leave, professors, assistant professors, I got a new doctor. She immediately took me off of Actos and put me on metformin, and then increased the dosage. I was taking 2, I think, grams a day, pill, morning and night, and my A1c kept climbing.

Along the way, I had checked a box to be selected for research, and I got a call from a Dr. Lingvay, an endocrinologist at UT Southwest, and asked if I would be in a study of about a new diabetic drug, and I may mispronounce this, semaglutide.

Anyway, I was on this study. It stared in April of 2016 through January of 2017. During this period, I think my A1c was 7.7. It went down to 6.5. I lost 30 pounds. And then I couldn't take it anymore because that was the end of the study. After I've been off of it, my A1c started creeping up. I'm in a blind study now, so I don't know what I'm taking. It could be the same drug, but it's a blind study that I started in June of 2017.

I was very pleased with the results but disappointed that I couldn't continue to have this drug available to me. I hope that this drug gets approved for the public because I think it has really helped, and I was very encouraged.

DR. WILSON: Thank you. Speaker number 6, please state your name and any organization you

represent.

DR. RODBARD: Good afternoon, Mr. Chairman, Dr. Wilson; members of the committee; ladies and gentlemen. I'm speaking here as an individual. My name is Dr. Helena Rodbard. I'm not representing any organization or any company. I'm a consultant for a number of different pharmaceutical companies and receive research grants. Nobody has paid my travel expenses.

I'm a clinical endocrinologist, and I have been in private practice in Rockville, Maryland for the past 35 years. Previously, I had been at the NIH-NIDDK where I had conducted clinical and basic science research in diabetes and endocrinology. In my practice, I have been specializing in the management of patients with diabetes, both type 1 and type 2, and have been engaged in clinical research to evaluate new forms of therapy for diabetes and lipid disorders.

Over the past 15 years, I have conducted more than 90 clinical trials, and I have published more than 120 papers in the peer-reviewed medical

literature.

During the past three years, I have had the opportunity to conduct clinical trials of semaglutide involving 24 patients. I have been tremendously impressed by the efficacy and safety of semaglutide. This is the most effective medication that I have seen in terms of achieving multiple endpoints: glycemic control without hypoglycemia, major reduction in hemoglobin A1c, weight loss, and also improvement in systolic blood pressure.

It's very well-tolerated by the patients with minimal side effects, and it was most gratifying to me, as a physician, to hear from my patients how much better they were feeling on semaglutide.

When the clinical trials were completed and the medication no longer available, every one of my patients asked if it would be possible for them to continue on semaglutide because they preferred it to their previous medications.

I had the opportunity to present data

regarding semaglutide at the annual scientific meetings of the American Diabetes Association and the European Association for the Study of Diabetes. Semaglutide represents a major advance in the treatment of people with type 2 diabetes, and I hope that it will soon be approved for the use in the United States and become available to my patients and to the diabetes community.

I wish to thank you very much for the opportunity to address you here today.

DR. WILSON: Thank you. Next, speaker number 7, please introduce yourself and any organization you represent.

DR. RATNER: Mr. Chairman, my name is Robert Ratner. I'm an endocrinologist and professor of medicine at Georgetown University Medical Center. I am not representing any group, and no one has provided any guidance or financial support for my being here.

We've talked earlier about the concept of patient-centered medical care. It is very clear that one size does not fit all, particularly when

it comes to dealing with patients with diabetes. The American Diabetes Association's standards of care actually provide a panoply of options for the therapy of individuals with diabetes beyond metformin therapy. And they provide guidance in terms of the characteristics that one has to look at in order to decide, with the patient, which medication is going to be most efficacious.

We need options, and we clearly need as many options as we can get to make sure that the individual can respond to the best therapy available. When you begin to look at the various drugs that are available to treat diabetes, the historic ones, sulfonylureas are very, very cheap, but they cause hypoglycemia.

We know that many of the other drugs, DPP-4 inhibitors, SGLT-2 inhibitors, are problematic when it comes to renal disease. We have to be able to individualize, we have to be able to pick the drug that is best for the individual patient, and that requires a broad spectrum of medications.

When one looks at semaglutide and the data

that have been presented here today, what you begin to see is remarkable impacts: a mean hemoglobin A1c against active comparators that's dropping 1.8 percent; 60 to 70 percent of patients at goal of 7 percent; a weight loss between 4 and 6 kilograms, again with 50 to 60 percent of patients achieving a 5 percent or greater weight loss. You see 70 percent of the patients in SUSTAIN 6 with underlying renal disease providing an option in that high-risk group, and 60 percent, in that study, with ischemic heart disease.

It's critically important that we have drugs that are efficacious, effective, and safe. But beyond that, we need to be able to discuss with our healthcare providers and with our patients with diabetes what the pros and cons are. Shared medical decision-making is clearly the appropriate way to go, and we can only do that if the information is available and if we can talk about it.

That really means full disclosure and transparency so that we can facilitate all of this

education and shared decision-making. Put the numbers in the package insert. Let us know what we can talk about in terms of both the safety, as well as the efficacy, and then the judgments become a discussion between the healthcare provider and the person with diabetes. Thank you very much.

DR. WILSON: Thank you. The next presentation by speaker number 8, please state your name and any organization you represent.

MR. MURPHY: Hi. My name is Dennis Murphy. I was in the once-a-week semaglutide study at the UT Southwestern in Dallas, Texas. In accordance with their company policy, Novo Nordisk has paid for my travel expenses to attend today's committee meeting.

Diagnosed with diabetes in 2004, I initially tried diet and exercise alone. Then I started seeing an endocrinologist and began trying multiple medications, including insulin with minimal success. I was exhausted all the time. My feet were burning while walking or exercising. My hemoglobin A1c climbed to 7.5, which is where it

was when I started this study.

Within the first couple of months of the semaglutide study, even at the initial lower doses, I started to feel a change. My feet were no longer burning, and I had lost about 15 pounds. My morning glucose readings were in the 80 to 110 range compared with the 170s before.

At the end of the study, I was taking once-a-week semaglutide, 30 milligrams of Actos, and 2 milligrams of glimepiride daily with a hemoglobin A1c of 5.7. If I did not tell a doctor I had diabetes before a blood test, they wouldn't even have known.

My time in the study felt like I was given a reprieve from diabetes. If the goal is to keep your glucose levels in the non-diabetic range to avoid damage to your organs, blood vessels, and nerve endings, and to give a diabetic a more normal life, semaglutide did that for me.

After the study ended and the semaglutide effect wore off, I was scrambling to find any drug that had an effect on the GLP-1 receptor. Over the

last two years, I've tried Tanzeum, Trulicity, and Bydureon, and none of them were nearly as effective as semaglutide.

I used Trulicity because it had the least negative side effects and combined with Actos, glimepiride, Januvia, and Invokana, I've been able to get my morning readings between 120 to 150, and my hemoglobin A1c has crept up to 6.5. The exhaustion and the burning feet have also returned.

I watched my father's body deteriorate during the 1970s and '80s after he was diagnosed with type 2 diabetes. I believe there was only one or two drugs available for treatment back then. I realize the longer I can keep my diabetes under control, the longer my vision and legs will last me. Semaglutide was a game-changer for me.

In conclusion, I think the numbers speak for themselves. During the study, taking once a week semaglutide, 30 milligrams Actos, and 2 milligrams of glimepiride daily, my hemoglobin A1c went from 7.5 to 5.7. As I speak to you today, my hemoglobin A1c is 6.5, even while taking once-a-week

Trulicity, 30 milligram Actos, 4 to 8 milligrams of glimepiride, 25 milligrams of Januvia, and 100 milligrams of Invokana.

I wanted to come before the committee to share my positive experience with the drug in hopes of expediting its approval, not just for myself but all those with type 2 diabetes still struggling to reach their goals. Thank you.

DR. WILSON: Thank you very much. The next speaker, speaker number 9, let us know your name and any organization you represent.

DR. POLANIN: Thank you for the opportunity to speak today. My name is Dr. Megan Polanin, and I'm a senior fellow at the National Center for Health Research. Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policy makers. We do not accept funding from the drug or medical device industry, so I have no conflicts of interest.

Patients with type 2 diabetes need safe and effective treatments to help them better manage the

disease and reduce the risk of diabetes complications. We agree with the FDA's assessment regarding semaglutide's efficacy and safety data but have several concerns that were not adequately addressed.

Number 1, while semaglutide met non-inferiority and superiority efficacy endpoints, there are clear differences between certain demographic subgroups. In placebo-controlled study 3623, the drug was less efficacious for participants of Hispanic ethnicity for both the 0.5-milligram and 1-milligram dose.

In contrast, the drug was less efficacious for participants of non-white race for the 1-milligram dose, but it is not clear which race, nationality, or ethnicity was driving this observed difference and whether any differences were observed specifically among patients within the U.S.

In active-controlled trial 3625, which compared semaglutide to basal insulin, the 0.5-milligram dose was less efficacious for men and

the 1-milligram dose was less efficacious for patients over 65 years old. The predominance of younger patients across studies is concerning as complications of diabetes increase with age.

While these demographic comparisons are interesting, they do not provide the information that patients and physicians really need or that the FDA really needs. Patients need to know if the benefits of this drug outweigh the risks for people like them. This would require separate analyses of these major subgroups to find out which types of patients are most likely to benefit.

Because the sponsor has not provided these analyses, we have concerns about the generalizability of this drug's efficacy and safety across subgroups. American Indian and Alaskan Native, Black, and Hispanic individuals have the highest problems of diabetes in the United States. However, these groups are disproportionately underrepresented in these studies, and there are too few participants from these subgroups to draw conclusions about safety or efficacy.

Number 2, outcomes in these studies are based on a biomarker, not a clinically meaningful endpoint important to patients such as living longer or quality of life. We know that glycemic control is controversial, especially for older patients. Low glucose levels can also put patients at serious risk. Let's keep that in mind as we consider safety data.

Number 3, we agree with the FDA that diabetic retinopathy is a safety concern. Studies were not long enough to investigate whether these effects will decrease over time, and as noted in the FDA ophthalmology consult, the assessment of diabetic retinopathy was not properly standardized and was not based on meaningful clinical endpoints. A longer follow-up should be considered before the FDA makes a decision about this serious adverse event.

Number 4, regarding cardiovascular safety, the sponsor has concluded that semaglutide risks are below the threshold of 1.8 and therefore non-inferior. One of the major goals of diabetes

treatment is to protect against cardiovascular disease, and there is doubt about whether semaglutide does so for all patients. Although not statistically significant, the rates of cardiovascular deaths, hospitalization for unstable angina, and hospitalization for heart failure are worse for patients taking the drug.

Moreover, major cardiovascular events are higher for women in these studies, and the sponsor has not studied the specific risk for women of color or women over 65, groups at higher risk for diabetes. Currently, it is unclear whether semaglutide should be considered safe for all women, and addition analyses should therefore be conducted before a decision is made about approval.

In summary, we urge this committee to recommend that the sponsor reanalyze the existing data to determine whether the benefits outweigh the risks for women of color, white women, men and women over 65, and other major demographic groups. We also recommend a longer follow-up with patients in the studies to determine safety, including

appropriate evaluation of diabetic retinopathy. If there are too few patients in major subgroups to meaningfully evaluate risks and benefits, the sponsor should be required to add patients prior to FDA making a decision about approval.

We urge this committee to consider the safety and efficacy of semaglutide within demographic subgroups and not subject patients to uncertain risk. Thank you for the opportunity.

DR. WILSON: Thank you. Speaker number 10, state your name and your organization that you might represent.

MS. CARRACHER: Good afternoon, and thank you to the chairperson and committee for this opportunity to speak on what I believe would be a groundbreaking development for people with diabetes.

My name is Ann Carracher. I'm an associate at Close Concerns, and I'm here to speak on behalf of the diaTribe Foundation, a nonprofit organization founded to improve the lives of people with diabetes, prediabetes, obesity, and to

advocate for action.

diaTribe, the foundation's patient-focused online publication, is subscribed to by over 130,000 people with diabetes and generates approximately 2.5 million page views per year. However, only 0.5 percent of those page views go to articles focused on GLP-1 agonists, underscoring the need for more awareness among both patients and their prescribing physicians of the benefits of GLP-1 agonists.

We believe that semaglutide, with the superior efficacy profile in patient-friendly once-weekly dosing, is a truly disruptive candidate that would go a long way in making both patients and providers more aware of the benefits of this class.

By Close Concerns' calculations, the GLP-1 agonist class grew 25 percent in 2016 to reach $5 billion in annual sales, and it's on track to hit $6 billion in 2017. Despite impressive financial results, however, a 2013 diabetes care paper found that only 5 percent of patients with

type 2 diabetes in the United States were prescribed a GLP-1 agonist.

This number has, of course, grown significantly since 2013, but the barriers to GLP-1 agonist treatment remain the same: high cost, lower than optimal reimbursement, and a lack of patient-friendliness, largely due to frequent and sometimes complicated injections. Notably Victoza has maintained market leader status by revenue since its inception despite once-daily dosing.

I would ask you to consider then a GLP-1 agonist with a new level of efficacy compared to existing GLP-1 agonists, both in glycemic and weight benefits, giving and average A1c drop of 1.8 percent and weight loss of 10 to 14 pounds most recently in SUSTAIN 7, all with once-weekly dosing.

Semaglutide could be a huge win for patients with type 2 diabetes, not to mention obesity and even prediabetes down the line. Semaglutide would join exenatide and dulaglutide as a once-weekly formulation, but the data show that it simply performs better as a GLP-1 agonist. It balances

efficacy and patient-friendliness in a way that no GLP-1 agonist has before. As far as injectable therapies go, semaglutide is also simpler to prescribe and dose than insulin and fixed ratio combinations making provider-friendly as well.

Moreover, more choices are better for patients and patient access. Assuming pricing similar to Victoza, we would imagine a high level of interest from both patients and providers. Perhaps most importantly, patient satisfaction and ease of use promote adherence. In a theoretical world, high adherence encourages reimbursement, meaning more patients can access breakthrough therapies like semaglutide.

Traditionally, the FDA has not concerned itself with matters of patient access. Still, we've recently seen Commissioner Gottlieb introduce the Drug Competition Action Plan with the goal of improving consumer access to medications. In this environment, the patient access implications of another truly disruptive GLP-1 agonist should not be ignored.

We fully believe semaglutide will shake up the GLP-1 class for the better and strongly encourage the committee to consider the benefit this would have for patients. I'm looking forward to the rest of the day's discussion and thank you again for this opportunity.

DR. WILSON: Thank you very much. We're skipping the number 11. I guess that's good luck, but we'll come back to that. Speaker number 12, please state your name, any organization you represent.

MS. DOVE: Good afternoon, and thank you for the opportunity to speak today. My name is Abigail Dove, and I'm an associate at Close Concerns. I'm speaking on behalf of dQ&A, a diabetes and obesity-focused market research company that provides pharmaceutical and medical device companies, as well as many leaders in the field, with insights into the patient perspective from a panel of 10,000 people with diabetes.

Today we have seen impressive clinical data on semaglutide, showing overwhelming benefit not

only for glycemic control but also a host of additional outcomes, notably weight loss, more time spent in range and out of hypoglycemia, and even a suggestion of a cardioprotective benefit.

I believe that the approval of this drug, with its impressive effect on these crucial outcomes beyond A1c, would represent an important step forward in diabetes care, offering patients a new level of efficacy to address the factors they care about most.

To this end, data from a series of recent dQ&A studies powerfully illustrate the importance of these beyond A1c factors to patients' feelings of success and how the majority of current therapy options, unlike semaglutide, aren't delivering on this front.

In a study soon to be published in Clinical Diabetes, dQ&A has surveyed nearly 3500 people with diabetes to assess their priorities when it comes to diabetes care and their perceptions of their current diabetes therapy regimens. The results overwhelmingly pointed prominence of time and range

and weight loss from the patient perspective.

Patients rated time spent and the ideal blood glucose range as the factor with the biggest impact on their daily lives. But despite the importance of this metric, only 25 percent of people with type 2 diabetes on insulin and 38 percent of people with type 2 diabetes not on insulin reported that their current therapies are very successful at delivering in-range numbers, avoiding the extremes of hypo and hyperglycemia.

Furthermore, despite the importance of weight management in diabetes care, current diabetes therapies fall similarly short in this domain. Only a small fraction of people with type 2 diabetes, just 10 percent of those on insulin and 17 percent of those not in insulin, indicated that their current diabetes therapies were very successful at reaching or keeping to a healthy weight.

Overall, dQ&A's data suggest that current diabetes therapy regimens don't deliver success to the majority of patients when it comes outcomes

like weight loss and keeping blood glucose in range and out of hypoglycemia, which matters so critically to people with diabetes. We see these as unmet needs that semaglutide, if approved, would certainly address.

Even more definitive evidence of the desire among patients for a therapy beyond A1c benefits of semaglutide comes from a newer dQ&A study. At the request of the diaTribe Foundation, dQ&A surveyed over 4,000 people with diabetes to assess their preferences for what matters most in a diabetes therapy, asking participants to repeatedly choose between hypothetical diabetes drugs with different profiles in terms of efficacy, side effects, and injection burden.

Using a statistical technique called conjoint analysis, from these data, dQ&A was able to mathematically parse out the relative importance patients place on these different features. The analysis revealed that people with type 2 diabetes were most compelled by a drug's ability to promote weight loss, closely followed by a once-weekly

dosing regimen, promoting more time spent in range, and a minimization of hypoglycemia. Surely, the study participants would be thrilled to learn that an existing therapy, semaglutide, actually has all of these qualities and more considering the evidence for cardioprotection.

As a member of the Close Concerns team attending dozens of scientific meetings each year, I've witnessed substantial excitement from clinicians regarding semaglutide as a potential best-in-class agent in the GLP-1 class. This is certainly remarkable, but as I see it, what's even more striking about semaglutide is the rare potential for the clinical enthusiasm surrounding this agent to be matched by equal excitement from patients themselves since, as these data suggest, semaglutide offers precisely the benefits that patients value most. This is particularly confidence-inspiring in terms of adherence, which has traditionally been a challenge for the nearly 40 diabetes drugs approved in the past decade.

As you make your decision on semaglutide's

approval, I hope the advisory committee will take into account on how strikingly this agent aligns with the preferences of people with diabetes. This truly is historic opportunity to make available a diabetes therapy with next-level efficacy not only for glycemic control but also for beyond A1c outcomes with critical importance in patients' daily lives. Thank you so much for your consideration.

DR. WILSON: Thanks very much. Speaker number 13, please state your name and any organization you represent.

MS. MARATHE: Good afternoon, and thank you for this opportunity to share my perspective on semaglutide. My name is Pyal Marathe, and I work for Close Concerns, a healthcare information company that aims to improve patient outcomes by making everyone smarter about diabetes and obesity. As far as disclosures, almost 304 and nonprofit organizations, including today's sponsor, subscribe to our fee-based newsletter called Closer Look.

The Close Concerns team, myself included,

attends more than 50 scientific meetings each year, conversing with a wide range of thought leaders in the diabetes and obesity fields. This exposure to the forefront of clinical research and to the latest clinical opinions on best practice diabetes care is what leads me to believe that semaglutide would be an enormously valuable addition to the diabetes treatment arsenal.

There seems to be little dispute in the community that semaglutide has shown profound and consistent A1c reductions in weight loss across an array of randomized-controlled trials. There's tremendous enthusiasm among clinicians, diabetes educators, and patients advocates for the GLP-1 receptor agonist class, one of the only downsides, being low adherence in the real world.

As we've heard time and time again, the best medicine on the planet won't do any good if a patient doesn't take it. IMS Health published a report last year showing that poor adherence is responsible for between 4 and 15 percent of diabetes complication costs incurred by the

healthcare system. In the U.S., this amounted to a grand total of $4 billion or more than $14,500 per patient lifetime.

Enter semaglutide, a once-weekly GLP-1 agonist that cuts injection burden into one-seventh or one-fourteenth. This is much easier for patients to take. Too often, real-world evidence doesn't match up with data from randomized-controlled trials because of forced adherence, but this is less likely to happen with once-weekly semaglutide. At Close Concerns, we can't wait to see the real-world findings on this very potent, effective therapy.

Even within the highly-praised class of GLP-1 agonists, semaglutide boasts potential to rise above the rest. One reason is the better adherence, and additionally, semaglutide has shown superior A1c reductions in weight loss in a head-to-head comparison with another once-weekly candidate already on the market, dulaglutide.

This impressive data speaks for itself, but I also want to quote one renown thought leader who

said a 0.4 percent A1c treatment difference is a thrashing in the head-to-head trial business, half a drug's worth. Importantly, this study found no correlation between semaglutide and diabetic retinopathy.

As best-practice diabetes care shifts toward more comprehensive approaches, providers are favoring therapies that not only lower A1c but that also improve critical outcomes beyond A1c, including body weight, frequency, and severity of hypoglycemia in cardiovascular health. Semaglutide shines on all of these parameters.

The agent seems to produce a new level of weight loss unheard of with current options for chronic weight management, demonstrating superiority even to high-dose liraglutide, another GLP-1 agonist manufactured by today's sponsor.

Obesity is a clear public health problem in this country in its own right, also inextricably linked to the type 2 diabetes epidemic. And it's vital that better therapies are made available to patients to support weight loss.

Semaglutide's glucose-dependent mechanism of action minimizes hypoglycemia risk, which is important because of the outrageous costs and because fear of hypoglycemia causes 72 percent of primary care physicians and 79 percent of diabetes care specialists to treat diabetes less aggressively than they otherwise would.

Based on these stats, it's no wonder glycemic control is suboptimal at the population level. But approving semaglutide would be a step in the right direction because you'd be adding a treatment option to the diabetes toolkit that efficiently lowers A1c without increasing hypoglycemia risk.

With all these benefits in tow, it would truly be a shame to keep semaglutide away from people with diabetes in the real world, especially when a singular safety concern could be well managed with proper patient selection, education, and monitoring for retinopathy risk factors. All of this, I think, could be clearly stipulated on a semaglutide product label.

Let's not forget that the base rate of retinopathy in small in comparison to the rate of patients above their 7 percent A1c goal. It's also small in comparison to the rate of obesity in the United States, higher than 20 percent in all states and territories, reaching 38 percent of the adult population in West Virginia according to the CDC's 2016 figures.

The impact retinopathy on patients should not be minimized but nor should severe unmet need for more effective anti-diabetes therapies like semaglutide. Very soon, I hope to see this medicine out there helping patients control their blood sugars and lose weight with easy-to-take once-weekly doses.

In closing, I'd like to again sincerely thank you for this time and for all the work you do to get safe, effective therapies into patient hands.

DR. WILSON: And we have one more speaker. Please introduce yourself and any organization you represent. Thank you.

DR. DARSOW: Thank you. Good afternoon. My name is Dr. Tamara Darsow, and I'm the senior vice president of research in consumer programs at the American Diabetes Association. The association represents over 14,000 healthcare providers and scientists, as well as the 30 million Americans with diabetes. I have no financial conflicts of interests on the matters under discussion here today.

The ADA does not testify in support of individual products, however, we do strongly support the need for continued innovation and research toward developing new therapies to address the many persistent unmet needs that exist for people with diabetes to further reduce diabetes-related complications and to improve quality of life.

Type 2 diabetes is a complex metabolic disease and is strongly associated with obesity as is illustrated by the close association between the increasing problems of the two diseases.

More than 80 percent of people with type 2

diabetes are overweight or obese, and we know that modest, sustained weight loss can produce clinically meaningful reductions in blood glucose, in A1c, and in triglycerides, and that greater weight loss produces even greater benefits. This includes reduction in blood pressure, improvements in LDL and HDL cholesterol, and reductions in the need for medications to control blood glucose, blood pressure, and lipids.

Weight loss-related improvements and glycemic control are most likely to occur early in the natural history of the disease and when insulin secretory capacity is relatively preserved. And consequently, lifestyle change with the objective of weight reduction is a cornerstone of diabetes management from the point of diagnosis.

However, lifestyle changes are difficult to implement for many people and even harder to maintain over the long term. And even when successful, lifestyle alone may not be enough to control blood glucose and risk factors associated with diabetes given, again, the natural history of

the disease. So weight management becomes an obstacle for many people with type 2 diabetes.

Another urgent unmet need in diabetes is the management of cardiovascular disease risk. Diabetes is an independent risk factor for cardiovascular disease, and people with type 2 diabetes are about twice as likely to develop CVD than people without diabetes.

CVD is also the largest contributor to the direct and indirect cost of caring for people with diabetes, and diabetes and cardiovascular risk factor management is typically addressed using multiple medications in combination treating hyperglycemia, hypertension, hyperlipidemia. However, despite significant advances in glycemic and cardiovascular risk factor management, still less than 20 percent of people with diabetes achieve treatment targets for A1c, blood pressure, and lipids, and significant residual cardiovascular disease remains.

Now we are entering into this era of having therapeutic options that improve outcomes beyond

glycemic control. With some antihyperglycemic medications demonstrating a favorable impact on weight, cardiovascular safety, and in some cases even cardiovascular benefit, for nearly 30 years, the American Diabetes Association has published our standards of care for diabetes, the preeminent evidence-based guidelines for the treatment of diabetes; and the standards recognize that the treatment of type 2 diabetes is not just about managing hyperglycemia but also the associated comorbidities such as obesity and cardiovascular disease.

For most patients, treatments that safely address hyperglycemia in the context of weight management and cardiovascular risk reduction are needed to effectively manage the disease. People with type 2 diabetes deserve access to advanced therapeutic options that address these unmet needs. Thank you.

Clarifying Questions to the Applicant (continued)

DR. WILSON: Thank you very much.

The open public hearing portion of the

meeting is now concluded, and we will no longer take comments from the audience. Really, thank you very much. It's a tough time of the day, and those were all excellent presentations.

The committee will now turn its attention to address the task at hand, careful consideration. But before we do that, we have to finish up some of our morning business.

The first is the morning carryover for some of the questions to the sponsor, and then secondarily after that, any data that we asked just before lunch. Carryover is from the sponsor. We have a list, and we're going to go down that list and see if they still have the questions in front of them.

Dr. Rosenberg, you're on the list. Did you have any follow-up with the sponsor, questions?

DR. ROSENBERG: Yes. Thank you. I think some of my comments have been addressed or at least we'll discuss them later, comparing the results of the study with the other study in terms of the diabetic retinopathy.

I've one question or concern regarding the HbA1c curves, and especially the very high level in the placebo group. We started around 9 and have very little decrease, and it's really very different or quite different from many of the other trials, including with liraglutide.

I wonder why this is the case, why it remains so high across time with results, data with all the meds adjustment, and how much that contributed to of course the delta. That has certainly consequence for us in terms of relating to the efficacy of the drug and also to the issue of the diabetic retinopathy. Any comment on this would be appreciated. Thank you.

DR. GOUGH: Thank you for that question. The full question I think this morning was not just the A1c but also why we're not seeing retinopathy in some of the other cardiovascular outcome trials. I think it's a function of A1c -- or the question related to A1c, but also more general in terms of the results of cardiovascular outcome trials.

Now, I think the first point that I need to

make is that there's a clear difference, and it's very difficult to compare between different trials, where they're not head-to-head and you're comparing different trials. There are clearly different characteristics.

We know that if we look at the different CVOTs, there were different populations, they had different A1c's, they had different baseline A1c's. For example, in SUSTAIN 6, we had no upper limit of A1c at the time of recruitment, whereas all of the other CVOTs did have an A1c restriction of either 10 or 10.5 percent. So we did have higher A1c's than has been seen in other cardiovascular outcome trials.

We have looked at the changes in A1c in other cardiovascular outcome trials. In the top left-hand corner, I, first of all, give you SUSTAIN 6. And then moving along the top line, you can see EMPA-REG, CANVAS, and then on the bottom line, we have LEADER, ELIXA, and EXSCEL.

I think the first point that I need to make is that with respect to the placebo group, we did

as well, if not better, with glycemic control in the placebo arm than any of the other CVOTs.

I can also tell you that in terms of our trial design and protocol, we did go to great efforts to encourage investigators to improve glycemic control in both treatment arms, including placebo. But what's evident, certainly from SUSTAIN 6, is that semaglutide was so effective in terms of lowering A1c, it was difficult, as you can see from the top left-hand corner, for any other alternative therapy, which included insulin, to come anywhere near the A1c reduction we saw with SUSTAIN 6.

But if you look at the gray lines, you can see that in terms of the A1c change to placebo, we haven't done any differently; if anything, slightly better than some of the other cardiovascular outcome trials.

Tying this in also to diabetic retinopathy, I think one of the questions that was raised was why have we not seen the diabetic retinopathy complications in these other CVOTs that we've seen

in SUSTAIN 6. And again, I go back to, one, our inclusion criteria, which was slightly different but not that different to some of the other CVOTs. But the important point is that we did retinal assessments.

I fully accept there are significant limitations with the approach that we adopted in terms of fundoscopy, but what that did do was prompt questions around adverse events. And I'm sure that's the main reason why we have more adverse events in relations to diabetic retinopathy in SUSTAIN 6 than the other CVOTs because we did a retinal assessment at 1-year and at 2-year. And I showed you the data this morning where you can see that most of the events, adverse events, were actually picked up at the time of those assessments.

I think finally, what I would want to say is that this early worsening that we've seen -- and I think this has been a theme that keeps coming back -- is not specific to semaglutide. This is a glucose-lowering effect. We have seen it with

insulin.

As Dr. Aiello has also pointed out, we've also seen it, for example, with bariatric surgery in type 2 diabetes where glycemic control has improved dramatically. It's also been seen post-pancreas transplantation where there's been dramatic improvements in blood glucose, and we're starting to see it with some of the other agents.

So this is not a semaglutide-specific effect. What we've seen in SUSTAIN 6, we believe is related to this glycemic effect, a highly efficacious drug similar to some of the other therapies or modalities I've just mentioned.

I tried to pick up a number of questions in that response.

DR. WILSON: Our next carryover is Dr. Low Wang.

DR. LOW WANG: Thank you. My question actually does have to do with this topic of the fact that there was not as much A1c lowering in the placebo group and how aggressive were site investigators instructed to titrate their

glucose-lowering therapy, and then also what glucose-lowering drugs were excluded from the trials, mainly SUSTAIN 6.

I guess looking at some of these other trials, these other cardiovascular outcome trials of GLP-1 receptor agonists, I looked specifically for any mention of AEs and SAEs related to retinopathy, and there was no mention of any signal. So I still don't understand that despite a couple of the trials having fairly similar lowering of the A1c, about 1 percent in a couple of them.

DR. GOUGH: Again, to take your last point first, I do think it's fair to say that in the cardiovascular outcome trials, they have not asked the question that has been asked in SUSTAIN 6. And they have not performed the fundoscopy assessment at 1 year and at 2 years that were performed in SUSTAIN 6 which picked up these events.

One of the things that I think is fairly clear, that if you don't ask the question and you don't look, you won't pick it up. Fundoscopy assessment, as we've heard, is far from ideal, but

it did at least prompt that process. And if you look at our adverse events in SUSTAIN 1 to 5, you can see they're consistent with what you would expect in terms of diabetic retinopathy adverse events with other clinical trials.

DR. LOW WANG: Could I actually turn that question around and ask, why did you look for retinopathy in the study? What signal was there that prompted you to include that as an outcome?

DR. GOUGH: Again, with hindsight, we can ask the question why we did look for retinopathy.

(Laughter.)

DR. GOUGH: I think importantly, we knew we had the glucose-lowering agent that was effective. And as we've heard, and we've heard from some of the public presentations, it's not just an effect on glycemia that's important; it's effects on diabetes outcomes including cardiovascular outcomes and microvascular outcomes.

As Dr. Hvelplund mentioned when he presented SUSTAIN 6, we have this composite. Again, you can ask the question, why do we have that composite.

But we had a composite of nephropathy and retinopathy because we believe that there would be a potential benefit. I think that's fair to say.

Can I address your first points, which were in relation to how did we try and ensure that the placebo group did have good glucose-lowering, but what lengths did we go to? And maybe I can call upon Anders Hvelplund just to take you in a little bit more detail into the protocol.

DR. HVELPLUND: With regard to SUSTAIN 6, I think it's important to point out that it was not a treat-to-target trial. There were individualized targets for the patients. They were not allowed to go on another GLP-1 receptor agonist, but apart from that, they were allowed to use all the other glucose-lowering drugs.

We did, throughout the course of the trial, send out global letters, including blood glucose treatment guidelines to all sites in order to remind them and to reiterate the treatment guidelines available. And that was followed up during the trial with global letters and direct

contact with sites on subjects that had inadequate glycemic control.

So throughout the trial, we tried to reiterate the need for glucose lowering for all subjects. And we did achieve that to some extent, but it is difficult when you do not use a GLP-1 receptor agonist to get as low as we have gotten with semaglutide.

DR. LOW WANG: Just a quick clarification. Were DPP-4 inhibitors also prohibited?

DR. HVELPLUND: They could not use DPP-4 inhibitors in the SUSTAIN 6 trial, no.

DR. WILSON: Dr. Li-Ng, did you have any questions that carryover for the sponsor?

DR. LI-NG: I think my only question was about TZD use in the 79 cases of the patients who did have diabetic retinopathy complications.

DR. GOUGH: Yes. We have looked at the use of thiazolidinediones in SUSTAIN 6 and specifically in patients with diabetic retinopathy complications, and I can show you those data here.

The top part of the table shows you the

total SUSTAIN 6 population and how many patients were on a thiazolidinedione when they came into the trial. You can see there were 14 patients in semaglutide 0.5 milligram, 21 patients in semaglutide 1 milligram, and 41 patients on placebo. There were 35 patients that used TZDs in SUSTAIN 6 on semaglutide and 41 in placebo.

If we then move down to the bottom table, you can see there's only 1 patient, and that was on a patient on the 0.5 milligram semaglutide dose and was actually also taking a thiazolidinedione both at the time of the event and actually throughout the trial.

DR. WILSON: Dr. Budnitz?

DR. BUDNITZ: Yes. I just had a clarifying question to make sure I understood the sponsor's proposal for addressing this retinopathy issue now that we have these data.

On page 19 of the background materials, it says "Risk minimization activities proposed by the sponsor include labeling with specific wording addressing the risk of retinopathy complications in

high-risk patients" in the warning and precaution section.

I'm not quite sure if I clearly understand who these high-risk patients are. Is it folks with preexisting severe retinopathy or what exactly do you mean by that?

DR. GOUGH: What we have shown with respect to a patient's developing diabetic retinopathy complications are that they are those patients with preexisting retinopathy. So clearly, there's the first category in which we have high-risk individuals. But in addition, it's those patients that had diabetes of long duration, patients with a high baseline A1c, and patients then that also had a high A1c reduction.

What we would recommend the direction of that label is to help clinicians who have a patient in front of them with diabetic retinopathy and also a high A1c so that they can then manage the glycemic control appropriately as has been highlighted by Dr. Aiello following standards of care in local clinical guidelines.

DR. BUDNITZ: Just to clarify, it's a little bit more than the standard warning that might be in an insulin label, you're suggesting?

DR. GOUGH: The proposed warning, or the warning that we would be proposing, would be a similar language to that currently used by insulins, and that specifically rapid improvement in glucose control associated with temporary worsening of diabetic retinopathy has been observed and that patients with a history of diabetic retinopathy should be monitored according to local guidelines, and that includes patients with varying degrees of baseline A1c.

DR. HIATT: I'm sorry to interrupt, but that's a warning. You don't want that -- that's where you want that in the label, as a warning; is that right?

DR. GOUGH: I think that the final label will follow on from discussions with the agency.

DR. HIATT: Sure. Okay. It's not a black box?

DR. GOUGH: No, that's not what we're

proposing.

DR. HIATT: I'm just clarifying.

DR. GOUGH: This will follow discussion --

DR. HIATT: Has there been discussion of a REMS program about this or not?

DR. GOUGH: No, there has not.

DR. HIATT: Great. Thanks.

DR. WILSON: Dr. Ferris?

DR. FERRIS: There were a number of questions that I had earlier, and we didn't get to any of them. Looking at outcomes by free form AEs, having spent a lot of time looking at free form AEs, is difficult at best. All one has to do is look at how they're reported across clinics to realize the differential reporting with regard to what Dr. Rosenberg was asking this morning.

I agree with him that with a sample size this big, randomization is likely to do a pretty good job of balancing out the severity or retinopathy. However, when the event rates are as low as this and, I would guess, irreproducible as this, the chance that random chance winds up

relating the outcome is pretty good.

In fact, I was saying to Jim Neaton earlier that this sort of reminds me of crowdsourcing in terms of the carefulness of the way this data was collected on retinopathy and perhaps goes to the power of the central limit theorem that this may be noisy data.

It may be true that there was early worsening. Actually, I couldn't say whether there was early worsening or not based on this data. I'd have to take randomization as the balancer in terms of retinopathy because retinopathy severity is clearly related to these outcomes, and whether there was confounding here by baseline discrepancy, I can't tell. And I'm still going back to this baseline retinopathy of 8.2 versus 5.2 percent. I just don't know. What is that?

DR. GOUGH: Just to clarify a number of those points that you've just made, first of all, I have to say that SUSTAIN 6 was designed as a cardiovascular safety study and that this was not designed as retinopathy study. That was not the

primary aim of the study. That's an important point.

We did look at assessment of retinopathy in a number of ways, and I accept that the assessments that we made were far from ideal, certainly in terms of fundoscopy examination. But what we did do is we did do a fundoscopy examination at zero, 1 year, and 2 years, and it was protocol-driven. It was included in the protocol. But the way in which we conducted that fundoscopy was not standardized in any way, which is a severe limitation of how we did that.

What it did do, as I previously mentioned, is it did give us an opportunity to actually identify more adverse events than would previously have happened and has previously been documented with other cardiovascular outcome trials.

We did perform fundoscopy. We also assessed baseline retinopathy status through the investigator. The investigator had the opportunity to obviously speak to the patients, ask them about their history of retinopathy, collect any

information they had in terms of retinal examinations.

In answer to part of your question of how did we know about the retinopathy status and proliferative retinopathy, that came through the investigator through the information that they collected from the patient, and not specifically from the fundus examination.

If that information was there and particularly if it came from a digital assessment using a fundal camera, we would have collected that information, but it was not standardized in any way.

In terms of adverse event reporting of the diabetic retinopathy complications, again, I would add that we then adjudicated those adverse events. They were collected for adjudication. Then that formed the basis of the main data. And that's what the diabetic retinopathy complications were, and they were evaluated by an independent event adjudication committee.

DR. FERRIS: Let me follow up on that for a

second. If there was an AE reported, you had an opportunity to validate it; is that what you're saying?

DR. GOUGH: If there was an adverse event and it was considered by the investigator to possibly related to diabetic retinopathy complications, further information was collected, and those source data were then sent to the EAC.

In addition, we did a search of our own, the MedDRA search. If anything was missed that could be possibly related to diabetic retinopathy adverse events, we would then pick those up, and, again, information could be collected and fed into the EAC. So the EAC received information from different sources, not just from the investigator but also from our search.

DR. FERRIS: I totally agree that the fact that you had an eye exam of some sort is likely to turn up more eye problems than if you didn't have. I get the false part of the positive. I get your ability to check the positives.

Are you suggesting that this MedDRA search

would pick up the negatives or false negatives?

DR. GOUGH: It would pick up anything related to diabetic retinopathy.

DR. FERRIS: If somebody wrote it down.

DR. GOUGH: If it was collected there was an adverse event.

DR. FERRIS: You did not have a form asking specific questions as I understand.

DR. GOUGH: In terms of adverse events, no, that was collected through the investigator and their assessment.

DR. FERRIS: And what about this 20 percent proliferative retinopathy I'm sort of stuck on?

DR. GOUGH: As I mentioned, that would have come from the investigator and his assessment of the patient in terms of whether the patient reported that's what they had or whether there was retinal examination information available to be scrutinized by the investigator. But again, I accept that this would not have been a compressive way of collecting that information. But it was the best that we attempted to do within a

cardiovascular outcomes trial.

DR. FERRIS: On the one hand, we're given 20 percent proliferative retinopathy. And if I'm reading this table right, it says based on retinopathy, any retinopathy -- I don't know what kind of retinopathy -- is 8.2 versus 5.2 percent. You understand why I'm having trouble with this data.

DR. SMITH: I think that was from our statistics presentation, the 8.2 versus 5.2 percent, although it might have been at yours as well. That's among the patients who were categorized as having baseline retinopathy, which you just had a conversation about.

DR. FERRIS: A [indiscernible] percent increase?

DR. SMITH: Then among those patients with baseline retinopathy, 8.2 percent in the placebo arm -- excuse me -- 8.2 percent in the semaglutide arm, 5.2 percent in the placebo arm had at least one event during the trial that was considered a diabetic retinopathy complication event, one of

those four.

DR. FERRIS: One of those four?

DR. SMITH: One of those four. It could have been more than one of those four. But that's patient incidence of at least one of those diabetic retinopathy complication events during the trial.

DR. FERRIS: Well, that doesn't add up either because there were only 79 events.

DR. GOUGH: No. Sorry, can I clarify that?

DR. FERRIS: Yes.

DR. GOUGH: In terms of the number of patients that we had and the number of events, there were 50 patients on semaglutide and 29 patients on placebo --

DR. FERRIS: That had events.

DR. GOUGH: -- that had an event. That's 79 patients in total, and there were 98 events within those 79 patients.

DR. FERRIS: I get that.

DR. GOUGH: And the majority of patients had a single event. So with respect to patients on semaglutide, 40 patients had a single event,

9 patients had 2 events, and 1 patient had 4 events. In terms of placebo, there were 27 patients with a single event, with one having 2 events, and one actually having 7 events, and the two patients that had 4 and 7 events were interventions.

DR. FERRIS: But that doesn't come anywhere close to 8 percent.

DR. HSUEH: The 8.2 percent is the event rate.

DR. FERRIS: What's the event?

DR. HSUEH: Okay. The numerator is the subjects with the event divided by the total number of subjects in that subgroup.

DR. FERRIS: 1648. Let's not do 8 percent. Let's do 10 percent. That's 168 events. It's not even close.

DR. CHONG: The 8.2 is only in the subpopulation with diabetic retinopathy with a baseline of -- I think we said 20 percent of the 1600 or something like that.

DR. FERRIS: Twenty percent of proliferative

retinopathy, according to this. Proliferative retinopathy, could that have been any retinopathy?

DR. GOUGH: To clarify, the 8.2 was the percentage of diabetic retinopathy complications from patients who had retinopathy at baseline.

DR. FERRIS: Okay. Well, if you had 20 percent with proliferative retinopathy, those with non-proliferative retinopathy in any kind of population, or 4 or 5 times that, is it possible that what was counted as proliferative retinopathy here was really any retinopathy?

If I remember, your categorization was normal, non-normal but clinically significant, and then abnormal, and abnormal and clinically significant. So you didn't really have proliferative retinopathy.

DR. GOUGH: Yes. Sorry. These two categorizations were collected two different ways. I'm sorry if we haven't made this clear. In terms of normal, abnormal, and clinically abnormal, that was in the opinion of the investigator based upon fundoscopic examination performed at baseline, at

1 year, and at 2 years.

So that's where that categorization came from. We asked the investigator, after the fundoscopy was performed, if they could then score the findings as either normal, abnormal, and if abnormal, whether they were clinically significant.

In terms of assessment of proliferative retinopathy at baseline, that came from the investigators' consultation with the patient in terms of what the patient told him or her and whether there was a report of a fundal examination performed at that time or within this previous 90 days. So those two bits of information were collected to separate ways.

DR. FERRIS: So the proliferative retinopathy came from history, not from exam?

DR. GOUGH: Exactly, yes.

DR. FERRIS: I would never ask a patient whether they had proliferative diabetic retinopathy. Most of them wouldn't -- I mean, it's not -- they know they have diabetic retinopathy.

I don't think I have any --

DR. WILSON: In the interest of -- we have several discussion questions, and some of these topics are going to be revisited. Before we go to start our discussion questions, was there, either from the FDA or from the sponsor, any further clarifications that you definitely wanted us to see before we moved into the discussion?

DR. GOUGH: We did have two further clarification points.

DR. WILSON: Okay. Could we quickly go through those?

DR. GOUGH: Yes. The first one related to the MACE events and the analysis of 122 events. Maybe I can call upon Darren McGuire to take that question.

DR. McGUIRE: Thank you. Darren McGuire, UT Southwestern Medical Center in Dallas. I am a professor of medicine there, a general cardiologist, clinical trialist involved in diabetes and cardiovascular outcomes trials, and maybe some clarity around some of the questions Dr. Hiatt asked. I asked the same questions as I

got introduced to these data. I was not involved in the design or execution of the SUSTAIN 6 trial.

Just going back to the concept of a trial designed to go until both criteria are met, 122 events and 2 years minimum follow-up. To be clear, all 3297 patients had been enrolled into the trial at the time the 122nd event was adjudication-confirmed, so there's no way to stop enrollment.

So at that point, it was destined to go to 2 years. And that occurred roughly around a median follow-up of 1 year. So the even rate was almost two times what would have been projected, and I have my own ideas about why that may have been, and you may have yours. I'd be happy to discuss it, if you'd like to ask questions about why the event rate was so much higher.

Then all patients would have 2 years. They didn't have to amend the protocol or re-consent the patients because that was the prespecified design of the protocol. And the conclusion is the same. The FDA may not have done it, but the first

question I asked the sponsor to do was let's analyze the first 122 events in this, here on the slide.

What you can see is there's a remarkable consistency between the first 122 adjudication-confirmed MACE events with an upper confidence limit of 1.01 that mimics the final analysis of 254 MACE events.

With these analyses, it would be my conclusion not only did the trial meet the primary specified non-inferiority exclusion of upper confidence limit of 1.8, it eclipsed also the 1.3 margin, which is the ultimate criterion for approval for cardiovascular safety, and in fact demonstrated statistical difference between the two groups with the 254 events that were accrued.

DR. HIATT: I really appreciate those data. That helps me a lot.

DR. WILSON: Okay. Anything further from the sponsor?

DR. GOUGH: There was one final question I think related to GFR. I'll call upon Anders

Hvelplund to take that question.

DR. HVELPLUND: We wanted to put a little more clarity in the context around the measurements we did in the SUSTAIN 6. First of all, with regard to eGFR, showing you here the mean eGFR over time in the total population, and as you may appreciate, we see the initial drop with the two semaglutide doses, and then they follow each other out to 2 years and not really a difference, as shown on top, between the 0.5-milligram dose and the placebo 0.5-milligram dose with an estimated treatment ratio of 1.00, and the same goes for the 1-milligram dose.

Then you asked with regard to splitting this up, and I can show you here, this split up with regard to renal function at baseline, you see around 30 percent with normal renal function in the top left corner, and then they're around 40 percent with mild renal impairment to the top right, and then the two lower panels show the more severely renally impaired.

As you may appreciate here, there does not

seem to be much of a difference when you look at least in those that have renal impairment at baseline, a slight difference with regard to those that have normal renal function.

This is also something we've seen in the other SUSTAIN trials, and we also see it for the comparators we have had in the other SUSTAIN trials. So that is a similar phenomenon we have observed with insulin, sitagliptin, and also exenatide extended release.

In all, we can say that we've looked at a broad range of renal function and shown both efficacy and safety.

You did also ask with regard to urine albumin/creatinine ratio, and I can show you that here, showing that from a baseline offset of around 40, we had an initial drop actually in the urine albumin/creatinine ratio, and then they were parallel throughout the course of the trial. Around a little more than half the patients had a normal albuminuria at baseline, and around 25 to 30 percent had microalbuminuria at baseline.

DR. WILSON: Before we move on, is that satisfactory response, Dr. Palevsky?

DR. PALEVSKY: It's a satisfactory response. I'd point out that in the normal group, that difference in GFR represents a very trivial difference in serum creatinine, so it would be extremely difficult to interpret.

DR. WILSON: Dr. Neaton, did you have --

DR. NEATON: Thank you. A couple of clarification questions. I'll start with the one on the diabetic retinopathy. Just to be absolutely clear there's no systemic difference being introduced into your calculations of incidents, these began with self-reported AEs.

Were these AEs collected throughout the 2 years of follow-up even if people went off treatment?

DR. GOUGH: Yes, they were collected throughout the course of the trial.

DR. NEATON: So they had to make a judgment as to whether or not the -- they did not have to make any judgment about whether those AEs were

related to the treatments under study.

DR. GOUGH: The patient made no judgment, no.

DR. NEATON: No, no, the investigator in terms of reporting them.

DR. GOUGH: They were all reported, but if they triggered -- there was also an instruction that if they hit one of these -- if they suspected one of the four criteria that I've mentioned in the DRC, then further information was collected.

DR. NEATON: And that's true even if people went off treatment in the first year of the study?

DR. GOUGH: Correct, yes.

DR. NEATON: The second question, this is maybe for you and the FDA. I'm not sure that I understood the term "retrieve dropout" for the hemoglobin A1c comparison. For example, this morning, I heard, if I heard it right, that in the sponsor's analysis, they only counted hemoglobin A1c events up until the time a person went off their study treatment or they went on rescue treatment. Is that correct?

DR. GOUGH: To take --

DR. NEATON: But you also said in your presentation that you continued to collect data just like for the AEs on hemoglobin A1c's. I didn't understand what you had to retrieve. It seemed like the data should have been there for the people that went off treatment and that also went on rescue treatment during the trial to do an analysis on.

I mean that's kind of what I would call an intention-to-treat analysis. It's not just the intention-to-treat population; it's basically counting the data throughout the entire period of follow-up, 2 years for your cardiovascular outcome study.

Were those data there, and that's what you mean by retrieve dropout, or did you actually have to go back and bring people back in and do measurements or something?

DR. GOUGH: To provide clarity on that, I'll call upon Lars Damgaard, my biostatistician.

MR. DAMGAARD: Lars Damgaard, Novo Nordisk.

The data were in the database. I guess the retrieve dropout is in the sense that they discontinued treatment, and as such, we are using the word "retrieve dropout" from treatment.

DR. NEATON: So you're just using the data now for post-discontinuation --

MR. DAMGAARD: Yes.

DR. NEATON: -- or post-rescue.

MR. DAMGAARD: Yes. What we are doing -- I can bring up a figure here, and just stop me if it gets too technical. Basically, we are grouping all the data into three groups. We have the group, on the left, group 1. That is subjects that, at the end of the trial, has a missing HbA1c value that we need to impute to maintain randomization.

Then we have the group 2. That is what we call retrieve dropout, and that is the patient that informed the imputation of the missing data in the first group. And that is subjects that has discontinued treatment, continued in the trial, and have provided a HbA1c value at the end of trial, week 30 or week 56.

Then we have remaining subjects that are not considered when we are imputing that data, but of course are considered when we are analyzing the data after we have done the multiple imputation.

DR. NEATON: Approximately how big was group 1?

MR. DAMGAARD: Group 1 in this analysis was in the range from 5 to 8 percent.

DR. NEATON: All right. Thank you. Just one question. I have to say I'm a little bit surprised that when I looked at the hemoglobin A1c curves that the FDA presented and that you presented, they looked almost identical.

So this other analysis seems to have made no difference in the sense that the placebo remains flat and the two treatment curves begin to slope upwards, and there's a bit of a treatment effect lost with longer follow-up.

Is that your interpretation?

DR. GOUGH: Yes. The multiple sensitivity analyses that were performed come to the same conclusion in terms of A1c and efficacy.

DR. NEATON: Also, it's not like a kind of improved effect on placebo. It's a flat effect on placebo and a loss of effect on the treatment over 24 months. That's the reason for the loss of treatment difference at 2 years versus the first 6 months.

DR. GOUGH: Could I just call upon Darren McGuire just to comment on that?

DR. NEATON: I'm speaking of the hemoglobin A1c measurements now, yes.

MR. McGUIRE: Darren McGuire, UT Southwestern. Just to be clear, SUSTAIN 6 was designed for glycemic equipoise, not an A1c-treated target. So you expect the curves to converge. And to the points earlier about poorly-controlled A1c in these high-risk cohorts, from a cardiologist perspective, we've been taught since 2012 in the guidelines that an A1c target of 8 percent or possibly higher should be the target in patients with advance cardiovascular disease.

So the placebo anchors at 8 percent because that's standard clinical practice in many places.

And then after the initial acute drop from the efficacy of the drug, the semaglutide-treated patients are being titrated off-label towards that same target probably.

I think SUSTAIN 6, it's tough to call that a loss of efficacy as opposed to the natural occurrence of a glycemic equipoised designed trial.

Questions to the Committee and Discussion

DR. WILSON: Thank you very much. We're going to go into the discussion period at this point unless there is any further need for clarification. We have lots more work to do here, as you're going to see.

We're going to do the discussion points one by one. For those of you who have the handout, there are four major discussion points. Topic 3 is the retina question. Let's go through these and pay attention to the words as I read each question that are emphasized and not get off-target so to speak.

We want good discussion for each of the items, but then we move on. The first one is going

to be related to glucose. I'm going to read it.

"The applicant has proposed that semaglutide be indicated as an adjunct to diet and exercise to improve glycemic control in adults who have type 2 diabetes mellitus. Discuss the efficacy of semaglutide with respect to glycemic control."

We're open for comments from the committee. This group is not pushing buttons. I'd like to hear some comment about in terms of people who with high levels, do they come down towards targets, for instance, of 7 or 8 for an A1c, and also some discussion about hypoglycemic risk. Those are the two things that immediately come to mind.

DR. BLAHA: I guess I'll kick things out with a fairly simple response. I was impressed by the consistent response and lowering HbA1c to clinically important levels. It seemed like the hypoglycemic risk was low. It seemed like achieving goal, the percentage achieving goal was favorable in the study.

So I was convinced that there was a benefit as an adjunct to diet and exercise for improving

glycemic control with this drug.

DR. WILSON: That was general. Any comments about hypoglycemia risk? Dr. Neaton, something else?

DR. NEATON: I don't have any comment about that, but I just want to say I'm pleased to see that the FDA carried out the analyses that they did because it confirmed what the sponsor had done because I think that's an important kind of a finding in terms of understanding those.

DR. WILSON: So your comment is that the FDA and the sponsor found similar results in terms of overall --

DR. NEATON: I'm very happy that the FDA convinced them to do the other analysis.

DR. WILSON: All right. Dr. Hiatt?

DR. HIATT: Like the others, it's hard to refute the efficacy benefit on A1c. It seems pretty dramatic and survived the sensitivity analyses because it's so large.

In terms of assessing hypoglycemia, I think the measures in the development program are

probably relatively insensitive to pick that up, adverse event reporting. And I think if it's really bad, you might have an excess risk of arrhythmias or cardiovascular events, which wasn't there either.

In terms of actually understanding the effect of hypoglycemia, it probably requires more continuous glucose monitoring or other techniques that I don't fully understand.

DR. WILSON: Thank you very much. It's great to hear cardiologists talk about hypoglycemia, but we have some endocrinologists here. Are the endocrinologists convinced? Go ahead.

DR. LI-NG: I was impressed by the efficacy results in terms of how robust the A1c lowering was in the setting of a low risk of hypoglycemia. I was also impressed by the sustainability of the A1c lowering even at 104 weeks. We don't see that sustainability with some of the oral agents such as the DPP-4 inhibitors. We did see that with liraglutide in the LEADER trial, so this is not

surprising. But again, I am impressed by the efficacy results.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: I would agree with that, with a caveat that it would have been nice to see a little more information about the general context in which this is achieved in terms of co-treatments and other level of risk and adjustment, especially what's happening in the control group. But it appears to be sustained with the limitations that we only have data up to 2 years, which will be a bigger issue for the other items to discuss.

DR. WILSON: Have convinced all the endocrinologists? Dr. Weber, Dr. Low Wang?

(Affirmative nods.)

DR. WILSON: Nodding approvals? Yes. Anything further from either of you? Dr. Low Wang?

DR. LOW WANG: I thought it was great to see this degree of A1c lowering, especially compared to another GLP-1 receptor agonist and some of these other agents that are available.

DR. WILSON: All right. Dr. Yanovski?

DR. YANOVSKI: Yes, I also agree that it was an impressive degree of A1c lowering, but this was also in the context of, I think, an impressive amount of weight loss. And I think it would be actually interesting to determine the degree to which maybe the weight loss was a mediator of some of this increase in efficacy in glycemic control.

DR. WILSON: All right. Can I summarize? Do we need any further on this? Let's keep moving onward. We got very strong opinions, favorable A1c across the board, very little risk of hypoglycemia especially compared to other agents in the class. A third key of point was the sustainability across the two years of experience.

Anything further? Those are the three key bullets. And I think, if anything, also, perhaps at least as good or perhaps better than some of the other GLP drugs in its class. It's at least one of the leading drugs in its class.

Can we go to the second discussion? Discussion question number 2, "Semaglutide once-weekly injection has been studied in 7 phase 3

studies and a 2-year cardiovascular outcome study. Excluding issues related to diabetic retinopathy and CV risk, which will be considered subsequently, discuss any safety concerns you have related to semaglutide, if any."

Now, I'll tell you my take on this one. If you go to the FDA 18 to 38, you'll see their slides. We're not going to pull those up, but those of you who have those. I'm going to quickly go through the topics, and it would be nice to have some quick consensus-building, what we think concerning gastrointestinal, gall bladder, kidney, immune, cancer, thyroid, blood pressure, and pulse, where there have been investigated differences in some things related to blood testing, related to these issues. But it would be helpful to have some comment for each of those.

The floor is open. Start wherever you want.

DR. PALEVSKY: I'll jump in on renal. I'm comfortable with the data provided. There does not seem to be any safety issue related to kidney disease.

DR. WILSON: And that means both eGFR change and albuminuria, Dr. Palevsky?

DR. PALEVSKY: Yes.

DR. WILSON: Others? Mike?

DR. BLAHA: Mike Blaha. I guess I'll take some of the cardiovascular -- non-cardiovascular outcome issues. I think the lowering of blood pressure, obviously generally speaking, is a good thing. It didn't seem to be there are any cardiovascular risk associated the blood pressure lowering, and probably it's only a benefit.

In the heart rate, a small raise in the heart rate seems to be consistent with what we see in this class and didn't give me a safety concern. From an other cardiovascular hemodynamic, I guess, endpoint, I was not concerned about the safety.

DR. EVERETT: This is Brendan Everett. I agree with that Dr. Blaha. I think the blood pressure sign is an important one. I suspect it's actually potentially mechanistically related to the reduction in stroke that was seen as a component of the cardiovascular OUTCOME trial. I think it could

also be driven, in particular, by the weight loss which I think is -- blood pressure tends to be particularly sensitive to weight loss. I'm not concerned about the changes in heart rate.

I think the gastrointestinal effects are obviously very important, but also it may limit the use of the drug broadly, but I don't see any concerns from an approval standpoint. I think the problem, of course, is going to be that many patients won't be able to tolerate the drug because of those side effects.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: I agree that I don't see any safety signal. I'm just a little concerned that the overall size of the database is limited to detect rare events, so we have to be cautious.

DR. WILSON: Anything further related to these -- we haven't heard some of these other topics. Yes?

DR. LI-NG: I was comforted by the fact that even though there was an increase in amylase and lipase levels, and calcitonin levels, they did not

increase to concerning levels, kind of relieving my concern about pancreatitis and other pancreas-related disorders.

DR. WILSON: Dr. Weber?

DR. WEBER: Just with regard to what Dr. Everett said, the nausea issue seems to be consistent with other studies. And I would actually postulate that that's a big reason for the sustainability of the weight loss that patients possible are chronically nauseated. I know quality-of-life data wasn't gathered in this trial, but one question that would come up is whether or not people will feel well on this drug. And their benefits from actually losing the weight that we've heard from some of the volunteers would be offset.

DR. WILSON: Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. I agree with the assessment about the issue of increased lipase, which I don't think is clinically significant. There's also no signal that I see for pancreatitis or thyroid cancer.

I did want to mention I saw just -- and I

wanted to second a point that was made earlier that this database is quite small, the safety database, for certain rare events, but there's a very, very tiny signal for possibly increased breast cancer maybe. And then also, there are more CAD and cardiac failure SAEs that were seen in the semaglutide group.

I think just to be cautious -- but we didn't see that manifested in the primary endpoint, so I wasn't concerned about the cardiac SAEs. I do think that in terms of monitoring for malignancies, especially the breast cancer, I would keep a watch on that.

DR. WILSON: Anything further?

(No response.)

DR. WILSON: Okay. I'm going to try to summarize. If we go down through the list, there was well-recognized gastrointestinal side effects, and that's been seen for this class of medications and a variety of comments about how that might actually help patients. But it should not be a barrier for use, and it appears to be seen across

the class, and it was rather expected, similar for gall bladder.

No concerns voiced especially after the most recent updating for the kidney and albuminuria data. Some concern, at least for -- this is a new class of medication -- to have longer surveillance for cancer safety, especially as been raised for breast cancer safety.

This class of drugs is being monitored for special increased risk of medullary carcinoma. The thyroid endocrinologists are aware of this. Other physicians are generally not aware of this, but that's for sure is likely to be continued as we go forward.

Our cardiology colleagues mentioned that the blood pressure effects appear to be favorable and may help to explain the stroke decreased risk and not much concern about pulse changes while on therapy.

Anything further on this?

(No response.)

DR. WILSON: Okay. Now, question 3, this is

really 3a. What can I say? They number things differently here in Washington. I guess those of us who live outside Washington get used to that.

Should I read all of it, the question, all the way through E? Should I do that? I don't know. I'll be honest. Can we do A? Thanks very much.

I'll read the opening part and then just A. Prespecified secondary safety endpoint was time from randomization, so the first occurrence of either a need for retinal photocoag, vitreous hemorrhage, treatment with intravitreal agents, or diabetes-related blindness. And the results for this composite endpoint, increased risk with semaglutide hazard ratio of 1.76, which was statistically significant.

So Part A is discuss the strengths and limitations of this assessment. And as you can see there, endpoint definitions, ascertainment, adjudication, trial design, other considerations.

Now, we've discussed this, so I think it would be helpful the first two or three speakers to

try to succinctly summarize some of what we've already discussed because we've already been going back and forth on this a fair amount.

This is open now. Who's going to go first? Dr. Ferris?

DR. FERRIS: I actually give the sponsor credit for trying to look a little more carefully at retinopathy. One of my rules of clinical trials is something worth doing is worth doing well; something not worth doing isn't worth doing well. This is sort of an example of something that was probably worth doing but wasn't done very well and gets them into trouble when you try to get to the details of looking at this as if it was a primary or important secondary.

However, the concept of saying, I want to look at clinically important outcomes in a randomized way systematically I think was pretty good. They have a randomized study, big randomized study. As Dr. Rosenberg was saying, I think it's likely that the retinopathy severity was balanced across groups. We just can't prove it because the

way they looked at it I don't think is adequate.

They're counting serious events, and they did eye exams to try to improve the ascertainment of these events, so I give them credit for trying. And we wind up with an imbalance. So now we've got this imbalance; what are we going to do about it?

Well, it's an imbalance, but it's an imbalance in the direction that we would have expected if you have a pretty large reduction in hemoglobin A1c between two groups. So it's consistent with previous studies, especially where there was a reduction of hemoglobin A1c of that size, albeit they were in type 1 patients.

Overall, I'd say they tried to do an assessment of clinically important events. They got an increased risk. That increased risk was consistent with previous studies, and I certainly wouldn't take that to mean that this probably shouldn't be put on the market.

DR. WILSON: Dr. Brittain?

DR. BRITTAIN: This probably couldn't have been known in advance, but at this point, the clear

shortcoming of the study was its length because we couldn't -- if, in fact, things are going to turn around after two or three years, we can't see that. Ideally, the study would have been four or five years and been able to make that determination.

So that was the clear limitation, although I can understand that it was not known at the time the study was being designed.

I also make the comment that I've heard a lot of people saying the assessment was not as good as it should be. But the fact that we're seeing a difference -- if it's a noisy assessment, if we see a difference -- I mean normally, noise makes differences harder to see, harder to detect.

I would be more concerned if we weren't seeing a difference in hearing that the assessment was noisy. But when you see differences when the assessment is noisy, that can be pretty convincing.

DR. WILSON: Dr. Hiatt?

DR. HIATT: I was going to say pretty much the same thing, that it's clear that the assessments may have been limited, but I don't

think it's ascertainment bias. And if it's a noisy assessment, that bias is to the null. So I agree with exactly what you just said, that if there's a signal in that context, then it's probably real. So I would view the signal as real.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: I'm not sure we can be completely certain that the bias at all was a null. It's likely. We know that this, given the nature of the study, cannot be really blinded. People obviously, participant and investigator, were obviously partially unblinded using HbA1c level.

So whether or not that leads to a better assessment in one group or another group, whether it's random or biased, we really have no idea. I would be cautious about that, and that's what worries me.

I guess the other, it's more or less for a future study. I don't know if it warrants asking the applicant to do another study or not given the context here and what we know from the literature. But if we really are concerned about an important

secondary endpoint, why on earth do we rely to adverse event collection to assess this endpoint? It should be collected as a primary endpoint or as a significant endpoint in a very rigorous manner, which obviously was not done there. And that really limits the interpretation of the results.

DR. WILSON: Dr. Li-Ng?

DR. LI-NG: I'm going to go to 3e and comment on my level of concern, related to the observed increased risk in diabetic retinopathy complications. I am not surprised by that early worsening retinopathy, and I'm going to relate this to patients that I see that are pregnant and diabetic because I follow a lot of pregnant diabetics.

When they come to see me in their first trimester, I don't tell them to not control their sugars because of their risk of worsening retinopathy. I tell them they must control their sugars to protect their fetus, and that there is an increased risk of diabetic retinopathy complications and that those are manageable. I

send them to the ophthalmologist, and they get checked every trimester.

I think that this data that were being shown, again, I give credit to the sponsors to be looking at this outcome. Does it make noise? It could be. But it does bring to light something that we as clinicians should be aware of, that if we are using a potent antihyperglycemic agent, such as semaglutide or even insulin, and we are improving glycemic control significantly over a short period of time, that risk of worsening retinopathy, as well as worsening neuropathy can occur. And for me, this kind of brings to light what I need to be discussing with my patients when I am considering additional therapies to improve their control.

DR. WILSON: Dr. Sleep, you had a comment? No? No. I'm sorry. I apologize. Dr. Del Priore?

DR. DEL PRIORE: Thank you. I just wanted to say that I think in terms of a question that's proposed in A, I think there are a lot of obvious issues, which people have brought up, in terms of

the assessments.

For the non-ophthalmologists in the room, part of the problem is that these are extremely subjective. There are criteria for applying laser photocoagulation, there criteria for applying anti-VEGF therapy. Does every ophthalmologist in the country follow the same thing? Does every ophthalmologist in my department follow the same criteria? No. There's a lot of variation.

So this is very different than what was seen in the CVOT trial where the endpoints are essentially acute MI, acute stroke, and death due to a cardiac event. It is problematic. I think that what has been said before, that there is a signal and it is in the direction that we think it should be in, I think are true.

Going back and redesigning the study, I think we could all probably think about lots of ways we can do a better job. But I do want people to remember that the endpoints that we're using actually are a little problematic. I suspect that the signal is real, and that it's exactly what we

expect it to be.

DR. WILSON: All right. In the interest of staying on course and given that we have five parts to this question, I'm going to summarize part A. Dr. Ferris started it off saying this was worth doing, but it wasn't done very well. I think that does summarize the thought of some of us, for sure, as we're listening. The assessments were subjective rather than some of the prospectively objective measurements that might have been refereed or adjudicated by other groups.

Dr. Brittain made a comment. If I can paraphrase, the shortcoming was that this study was short. She didn't say it quite that way, but that's what she said.

There was controversy about whether we have biased towards the null or away from the null. But the simplistic word is we had subjective assessments, which make it difficult to draw firm conclusions.

At least one of the committee members said perhaps a targeted study is needed to address this,

but we didn't get any further into that. One of our committee members mentioned there may be special groups for which we should be very concerned about, and since that hadn't come up, I put that in this section here as pregnant patients. One of the summaries was that the study was done using subjective assessments.

Let's move on to part B. "One hypothesis regarding this finding is that rapid and large reductions in A1c can be expected to increase the short-term risk of diabetic retinopathy complications. Discuss the extent to which you are convinced that a reduction in blood glucose or A1c is the mediator of the observed increase in diabetic retinopathy complications in SUSTAIN."

If you remember from this morning, we saw a data analysis that was looking into how much of the difference was associated with the glucose lowering of the molecule versus potentially other effects. The issue is a mediation -- part of it is, the mediator of the observed increased in risk for retinopathy, was it glucose or potentially other

aspects?

Any comments? Our statisticians can help us here. What can I say?

DR. FERRIS: I thought it was interesting that when you did the analysis to adjust for change in blood hemoglobin A1c, it drove the result or the relative risk toward 1. So that analysis was consistent with the hypothesis.

DR. WILSON: Dr. Neaton?

DR. NEATON: I would say we don't know, and basically -- this morning, Rick, you said there were 12 hypotheses you could come up with, so it goes beyond this class of drugs. I guess I go back to some of the discussion on the last question.

I'm surprised, given the hypothesis that it's related to glycemic control and we have new drugs that do a much better job at that, why there aren't some more focused studies on actually what the incidence is with a better instrument, both short-term and long-term.

So I think the answer to this question is we have no idea, and also if it's related to that,

whether it's going to disappear in three years.

DR. WILSON: Dr. Budnitz?

DR. BUDNITZ: Similarly, I think I'm convinced that glucose control is a mediator, but is it the only mediator? I don't know if we can know, and that's why I was trying to look at comparative, other CVOT trials with other drugs in the same class, or other CVOTs that had the same reduction in A1c levels.

You also have to have similar populations and risks, and it doesn't seem like we have any studies, at least, that were presented today, that we can make that kind of comparison to try to tease out if there is, at least indirectly, some other drug effect or it's just improvement in glycemic control.

In the end, it probably doesn't matter that much because you probably can't tease out the differences, so it does need to be identified anyway. And I guess for the long-term effect, you just need longer studies as Dr. Brittain said.

DR. WILSON: Dr. Low Wang?

DR. LOW WANG: I have to say that I am not convinced that the reduction in A1c is the only mediator, just as Dan said. But I think the analysis that was done, the post hoc analysis looking at the mean change at week 16 in A1c was a post hoc analysis, so that's a flawed analysis.

Then the other thing is that I think that what could have been done, now in retrospect or maybe prospectively in the future, is that the way we could answer this question definitively is trying to maintain the same A1c in both groups.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: I agree with Jim and the other comments that we don't know and really no way of knowing based on the existing data. My level of conscience in this is just, I would say, very moderate based on what I've heard from my colleague ophthalmologists and endocrinologists, which is based on the results of old studies, mostly in type 1 diabetics. And having not heard about a clear mechanism, that leaves me a little skeptical and uneasy.

DR. WILSON: Any further comments? Yes, Dr. Hiatt?

DR. HIATT: I'll let up with the, don't-know school of thought, but it keeps company with a label warning with insulin therapy. I did look up before the meeting there are some mechanistic studies looking at reduction in blood sugar in animal models with insulin leading to production of VEGF and HIF-1 alpha that can cause leaky membranes, not to say that relates to this necessarily. I think that it probably has a component of a degree of glycemic-control relatedness, but that's only by association.

It's interesting if you look at the patients with preexisting retinopathy at baseline, the number needed to harm is 33. If you calculate that same for the dose without preexisting retinopathy, the number needed to harm is 333, so 10-fold more. Clearly, there's a high-risk group that can be identify I think through labeling to guide clinicians as to how to pay attention to this.

My thought is, is I think a component of

that association is probably a reduction in A1c, but I wouldn't say that's conclusive. It's associative.

DR. WILSON: Dr. Weber?

DR. WEBER: There's been some discussion about mechanism, and actually I went to the literature and looked at GLP-1 and the eye. And it turns out there's actually salient effects in animal models involving the blood-retinal barrier. So how do we reconcile this counterintuitive discussion as to why it's harming when we have actually data that it's suggesting there may be some benefits? I think that's important to consider in the context of this discussion.

DR. WILSON: Dr. Blaha?

DR. BLAHA: Mike Blaha. Must of what I was going to say was actually covered by others, including Dan. But I would just say, as far as the written question here, I'm not convinced -- I don't think any of us can be convinced as in within 100 percent certainty that the mechanisms reduction of blood glucose is the mediator, although I

thought the analysis that the sponsor did was interesting. It's difficult, of course, because what does the drug do? It lowers A1c's. If you adjust for A1c, you kind of adjust for the drug. But still, I'm reassured that that analysis shows what we would have expected.

While I'm not convinced also as a cardiologist who didn't know this data, I am convinced by the DCCT data, which I didn't know just as someone not in the field. It lends me comfort that I think it's possible that this is all an A1c effect. And the DCCT data, thank goodness, we have it, or else we'd be quite confused here.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: Going back to the comment that we probably can identify a high-risk group, mainly if the patients were preexisting retinopathy, I would probably agree with this comment, although there are some problem of definition of who exactly is at risk. Is it the proliferative one or everybody? I don't think we have the data, given the discussion about the

definitions that we had.

There's also problem of the generalizability of the results given that a great majority of patients, in this trial at least, had predefined retinopathy to start with. Although the rates in the other who didn't appear very low, we, again, have to be cautious about generalizing to every diabetic in this country.

DR. WILSON: All right. Let's get a couple more comments on just the mediation because we're going to move into the other discussion points. Anything further explicitly on mediation? Yes, Dr. Low Wang?

DR. LOW WANG: I just wanted to say that even in that post hoc analysis looking at the A1c reduction at week 16, one of the arguments that was made is that the greater the A1c reduction, the higher the risk of retinopathy that was seen.

Looking at this graph in the sponsor's slides, it looks like even the people with lower degrees of A1c reduction, so less than 0.5 or 0.5 to 1.5, there was a higher incidence of retinopathy

seen in those patients that were on semaglutide. I don't know what that means because the group is very small, but it's a signal.

DR. BRITTAIN: So again --

DR. WILSON: I'm sorry, Dr. Brittain.

DR. BRITTAIN: I'm sorry.

DR. WILSON: We want to recognize you.

DR. BRITTAIN: You pointed at me. I think the data, the analysis, they did showed that this hypothesis is plausible, but it's far from convincing. I also noticed the data that Dr. Low Wang just mentioned. I was thinking about that as well. I also notice that the curves, the Kaplan-Meier curves, are showing no sign of coming together at all, for what that's worth.

This is more a final question. It's hard for me to evaluate the relevance of the DCCT data. Obviously, it provides potential comfort, but I don't know, without having data past 2 years, what we really know.

DR. WILSON: Can I summarize this part? We still have two or more sections of 3. I'm trying

to take the highlights.

Our statisticians said we just don't know how this works as a mediation, and they're often the people we always turn to for mediation analyses. The clinical investigators used various words, and they didn't find any of them successful. Is "a" mediator, "the" mediator, didn't like the word "only" mediator. It kept being reemphasized that this is a post hoc analysis for mediation.

We wrestled, the endocrinologists especially who say I think we've been wrestling with this, along with retina specialists, this is counterintuitive, this first two-year effect, and perhaps we need much better data to provide more convincing results.

A variety of points were made even small differences in the treated arm had retinopathy progression. I like Dr. Brittain's final statement there, mediation plausibility but not convincing at this point.

Let's go on to the next part. "Improving glycemic control should be expected to reduce the

risk of retinopathy over the long term." And that's not defined. I guess that's up to us to define.

"Discuss whether the increase in diabetic retinopathy complications in this two-year controlled trial affects your assessment of the clinical benefits expected from long-term use of semaglutide for glycemic control."

The issue here is length and something beyond -- or data beyond 2 years and how it would help us. Dr. Del Priore?

DR. DEL PRIORE: I don't think that there's anything surprising if you look at the DCCT results, but I don't think you can tell if these curves are going to cross because you just don't have the long-term follow-up. I think it's our expectation that they might, but in the absence of longer follow-up, we actually don't know if this effect is going to go away or not.

DR. WILSON: Dr. Palevsky?

DR. PALEVSKY: I would agree with that, and I would add that since we don't know the mechanism,

it's plausible but not proven that it was due to the rate of decline in hemoglobin A1c. We don't know that the mechanism that was postulated for DCCT would continue to apply. And the only way to know would be to have longer-term data.

DR. WILSON: I'm going to take Dr. Everett first. Dr. Everett?

DR. EVERETT: Yes. I think we have to be a little bit careful. There's a relatively large body of epidemiologic evidence, kind of post hoc analysis of trials, which suggests that there's an early increase in retinopathy with aggressive glucose control that then ultimately benefits patients in terms of reductions in retinopathy.

Given all the caveats that everybody has mentioned about the ascertainment of these endpoints, the validity of these endpoints to an ophthalmologist, we have to be careful of I guess throwing all the prior data out. So I think we have to maintain some degree of confidence that the long-term effects of hemoglobin A1c reduction and glucose reduction will have important effects on

the occurrence of diabetic eye disease.

The caveat here, I think, again, is that this is really the only study out there with this particular class of medications that's shown any data on retinopathy. Unfortunately, it doesn't go the way we'd like, and the study was stopped after 2 years for other reasons, so we can't know if these curves begin to track together or to cross as we would hope that they do.

It's a long way of saying that I agree that I think we should be optimistic and hopeful that the improved glycemic control offered with this agent will allow for improvements in the occurrence of diabetic eye disease.

It's really difficult to be sure, and there's not a small chance that these curves will continue to be separate, either because the early changes don't ultimately end up being reversed or because there's an alternative mechanism that isn't just hemoglobin A1c-related that we don't yet understand or haven't identified that is particular to this class of medications.

DR. WILSON: Dr. Ferris?

DR. FERRIS: I agree with Jim that I'm not sure we know whether there is an increased risk. I am sure that we don't know what's going to happen after 2 years based on this data.

Given that, I would ask everybody to look at this risk that we're talking about which is a 1 percent risk in a problem that has a high prevalence with or without this drug. And I think, as was suggested here, we don't know whether this is a glucose effect. This could be some kind of drug effect that's a direct drug effect on retinopathy.

However, we do know that this drug seems to be able to help reduce hemoglobin A1c, and there's a ton of evidence saying in the long run, multifactorially, that's important for these patients. So it seems appropriate to me that you give people a warning that, as you were talking about for pregnancy, this may be a factor and worrisome related to retinopathy, and so you ought to see your eye doctor. It's a pretty easy

message.

DR. WILSON: Dr. Neaton?

DR. NEATON: This is really more of a question. The one thing that I did find reassuring -- I'd be curious what the ophthalmologist thought. I don't remember the exact numbers, but I believe there were 5 versus 1 in terms of the counts of the participants that were legally blind, I guess, at one point. And it was a follow-up, and I thought they had said that three of the people in the follow-up, their vision, at least, had been partially restored with long-term follow-up.

So is that kind of somewhat reassuring?

DR. FERRIS: They had 16 vitreous hemorrhages. I bet there were more than five that at some point were less than 2200. They said three of them recovered. Some of them may have been seen at the last visit, so we don't know whether they recovered or not.

Most patients with vision loss these days, either through anti-VEGF or vitrectomy, recover

vision, and Lord knows what this blindness means. Obviously, whenever you see blindness, you worry about it. But given the way this data was collected and given the opportunities for intervention, and given other causes -- I mean I mentioned vitreous hemorrhage, but we don't know whether some of these people developed cataract associated with their diabetic retinopathy.

DR. WILSON: Let's start with you, Dr. Li-Ng. Go ahead.

DR. LI-NG: I actually was quite fascinated by a slide that Dr. Aiello had put up in terms of the patients under the intensive control in DCCT had early worsening, and it kind of leveled off, and those that didn't have early worsening ended up having still lower rates of worsening retinopathy.

I wanted to bring up the point that not every diabetic gets retinopathy and there are certain genetic factors, and obviously environmental factors, that put them at risk for diabetic retinopathy. And I actually wanted to ask the ophthalmologists whether there's anything that

you have noticed in their OCTs or something that kind of identifies -- you know that this patient is going to have to come back for laser, anti-VEGF, because you get those diabetic patients who just keep getting worse even with good glycemic control.

Again, I just want to keep in mind that not every patient is going to have worsening diabetic retinopathy. And those that will, they always seem to get worse, and sometimes it doesn't matter what you do.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: It would be nice if we could personalize treatment to those who are most likely to benefit, but it doesn't look like we're there quite yet.

Just to answer this question there, it does affect the assessments because we have a paradoxical situation where we know -- I'm convinced as others -- that there's been an epidemiological association between HbA1c level and the risk of microvascular and probably macrovascular complications. And that's why we

do want to keep the glucose levels lower.

Here, we are in a situation where we have somewhat paradoxical increase in the complication we want to decrease in the long term. And as we've said many times, there's no way we can know for sure, whether it's transient, it's a class, a drug effect, or what else?

We have purposed a trial with an objective of lowering HbA1c, but for a given purpose. But this purpose is not achieved in this study; it's the opposite that is achieved. And the cardiovascular effect, we'll talk about that later.

DR. WILSON: Dr. Weber?

DR. WEBER: Just to kind of expand on some comments about the potential comfort we have with the DCCT results. We aren't talking about a much younger population. And even though their length of diabetes was similar I think to this trial, there may be inherent differences in aging biology as it relates to metabolism and inflammatory biology specifically that may put them at higher risk for progression or for those curves not to

come back together. So it's a point of caution as we start to think about the application and comparison of the data.

DR. WILSON: Dr. Yanovski?

DR. YANOVSKI: Sure. I've been reassured that the proliferative retinopathy appears to really be manageable now with treatment. And there are guidelines from, it sounds like, professional societies for, for example, when you start intensive glucose-lowering therapy for having more frequent assessment. So I find that also reassuring and a manageable risk.

That being said, I would like to see studies -- and you'd have to figure out how you do these. I don't think they'd necessarily be RCTs, but studies that really do have good ophthalmologic assessments and that do follow patients long term so we can get a handle on not only whether this really is a problem but what the mechanisms might be.

DR. WILSON: Dr. Robotti?

MS. ROBOTTI: Hi. Speaking as a consumer,

from a patient's point of view, I find this very confusing. And I'm imagining sitting at a doctor's office hearing that, well, you got to keep your blood sugar down because diabetes puts you at a high risk for retinopathy, and you have diabetes, so you get retinopathy, and a significant amount are going to die of cardiovascular disease. But here's a drug I want you to take and it's pretty likely going to increase your retinopathy in short term, we don't what it's going to do long term, and it increases your cardiovascular risk.

So I'm confused here, so feedback is welcomed.

DR. WILSON: Thank you very much, Dr. Robotti. You're the patient representative. I apologize, but you help us a lot.

Dr. Rosenberg, did you have another comment?

DR. ROSENBERG: It's a kind of follow-up on the theme that we have to be careful. And, again, I rely on my colleague endocrinologists and ophthalmologists; if this drug is released on a wide scale, how sure, even for the people that are

at high risk, that they're going to come back for their regular evaluation and have this treatment that potentially can address this problem?

We know that a lot of patients are not always very compliant in this. They're happy to have the treatment once a week, and how good is the follow-up even on those high-risk patients?

DR. WILSON: In the interest of time, we still have a couple more bullets to shoot, so to speak, at this question for discussion. I'm going to try to summarize where we are at this point.

The issue of longer term -- and I think we arbitrarily defined something longer than 2 years is longer term; and some of the other studies have had three years and some have had four years, but certainly longer than 2 years -- there's a lot of concern about the contradictory evidence. As Dr. Rosenberg said, we expect one thing on the glucose, and when we don't get a favorable effect on retinopathy.

Well, this has been seen in the studies that have investigated retinopathy, but we harken back

again to the concern these are subjective assessments of retinopathy. And our ophthalmologists remind us you can't know what's going to happen after 2 years until you formally study after 2 years.

The comparison to the DCCT, we've had two studies that really were mentioned, UKPDS, a little bit the KROC, and then the DCCT. One has been a type 1 trial; the other is -- both of these are older trials. We have a modern era. We have very effective photocoag injections, et cetera, to save eyesight. But we still don't know the answer to progression and what's going to happen at the different levels.

I think one of the things that we should highlight -- and Dr. Yanovski brought this up for a potential follow-up study -- is it's different whether you have baseline disease or if you don't have baseline disease. So the long-term -- all the ophthalmologists have echoed this all along -- is that the rates are very different depending upon where you start from. The relative risks may be

somewhat similar, but the absolute differences are very different depending upon when you start out with the eyes with very little in a way of retinopathy.

Finally, I want to thank Dr. Robotti saying she's confused. Endocrinologists, cardiologists, statisticians, this is a complex field, and it's not simple, and I'd like to think we need more data to address some of these questions.

Can we go on to the next one? It's part D.

"The increase in absolute risk of diabetic retinopathy complications was greater in those with diabetic retinopathy at baseline 8.2 percent in semaglutide, 5.2 percent placebo compared to those without diabetic retinopathy at baseline 0.7 and 0.4 in placebo.

"Although the relative risk increases were similar, patients with diabetic retinopathy are often among those most in need of improvement glycemic control. Discuss whether you have any concerns about the use of semaglutide among these patients, if approved."

We discussed some of this, so maybe we can do this relatively efficiently. Yes, Dr. Hiatt?

DR. HIATT: Yes, just a couple of quick comments. I think the pretest probability of having diabetic retinopathy is based on your baseline assessment, and it's a 10-fold difference in that number needed to harm. It's pretty clear.

So I think you would not want to withhold this therapy in those patients. You want to inform the treating physician to diligently monitor this potential side effect, and there are effective treatments for it.

Secondly, if you look at the OUTCOME trial where this is best studied, they have 79 cases of retinopathy. There were an excess of 21 events on drug. That's not a lot of events, so the absolute event rate is still not huge. I think we have to put it in that context as well.

So I would not withhold therapy, but I would say that physicians should be aware of that and take appropriate measures to monitor their patients accordingly.

DR. WILSON: Dr. Blaha?

DR. BLAHA: I echo what Dr. Hiatt just said. I think it's ironic. It argues for all of us to be treating, of course, diabetes earlier because of course if we treat diabetes earlier, we prevent the retinopathy in the first place. Once the person has retinopathy, of course, that maybe could have been prevented ironically with A1c lowering in life.

I think we're hopefully moving to a point we're going to intervening earlier and reducing the baseline rate of retinopathy in the first place. But I think it does certainly serve to warn physicians who are treating patients with existing retinopathy that those patients need to be screened more carefully. I think that's the bottom line with that.

DR. WILSON: Dr. Low Wang, you had a comment?

DR. LOW WANG: Thank you. Looking at this question specifically, I think thinking about the different glucose-lowering therapies that are out

there for patients with diabetes, we have this result from the secondary endpoint analysis from the study that shows increased risk of retinopathy in patients, more so with the patients with baseline retinopathy. So I would be concerned, and I think that there are other choices out there.

DR. WILSON: I have a question to our ophthalmologic experts. If such a project were to be done, or a registry, or a trial -- I'm just thinking forward as we go through the rest of the discussion -- what would be a preferred way to go forward?

We mention so far in this monitoring the high-risk patients. And Dr. Hiatt was pointing towards the high-risk patients, especially being the person with baseline retinopathy.

Could our ophthalmologists tell us how they might suggest -- I'm sure there are many ways to do this -- the baseline disease burden of retinal disease. Dr. Ferris?

DR. FERRIS: First, there was a discussion earlier about risk factors for progression. There

are two important risk factors for progression: level of hemoglobin A1c and current level of retinopathy. And already -- Emily showed the table -- the more severe your retinopathy level, the more frequent you're suggested to see the ophthalmologist.

With regard to the difference here, remember, we're looking at endpoint complications. If you start with no retinopathy, in 2 years, you're not going to get to vitreous hemorrhage, unless this drug was doing something horrible, which we don't have any evidence of. In fact, we were just looking -- the five patients who were blind all had laser treatment and proliferative retinopathy.

So it's pretty clear to me that it actually isn't a mixed message; it's a pretty simple message. And the simple message is the lower your hemoglobin A1c, at least up to a point of ACCORD, the better off you're going to be. There may be some increased risk of retinopathy when you lower your hemoglobin A1c or maybe beyond, and you need

to see an ophthalmologist. The more severe your retinopathy, the more frequently you ought to see your ophthalmologist. And if you start on this drug, like getting pregnant, maybe you ought to see them in the next three months or six months.

DR. WILSON: So to simplify that, to see an ophthalmologist with a clinical assessment of the retina, with what procedure? Just a regular ophthalmic visit? That's where I was going.

DR. FERRIS: Yes. The thing that's going to drive what happens is what the ophthalmologist sees. The more severe the retinopathy, the more frequently they're going to need to be seen.

DR. WILSON: I think this is important. Dr. Del Priore, could you help with this?

DR. DEL PRIORE: Yes, I'd be happy to. I think the key is to have a baseline examination. And I think the analogy with managing patients who are pregnant is really a good one. I think that message has clearly gotten out. I very seldom see patients who have gone through a whole pregnancy without ever seeing an ophthalmologist. That

message is clearly out there.

Whether or not the other message, which is that as patients are put on a medication, either this or another one, that changes their glycemic control very rapidly, whether they should be seen at baseline and then quarterly or anywhere near that frequent depending on the findings. I don't know if that message is uniformly out there.

The ophthalmologists certainly know it, but we're not referring the patients to ourselves. So I don't know if the endocrinology community knows that or not or whether that's already being one. I don't usually see patients before they've been started on therapy or intensive therapy.

DR. WILSON: I guess maybe it's pushing it, but I was going, would fields 1 and 2 for the ETDRS with the scoring of photos and that in the chart, is that adequate or do you need to see an ophthalmologist? That's where I was going. That was the question to the ophthalmologists in the back of my brain. Each of you are saying see an ophthalmologist.

DR. FERRIS: Well, telemedicine is telemedicine, and that can be a way of assessing retinopathy severity, and I wouldn't be against that. But one way or another, you ought to get your retinopathy checked.

DR. WILSON: Thank you. Dr. Palevsky?

DR. PALEVSKY: Paul Palevsky. Just to reemphasize the point that the five patients who developed blindness in the semaglutide group all had documented proliferative retinopathy and had either received laser treatment or intravitreal treatment at baseline before starting drug, so clearly a high-risk group who needed frequent ophthalmologic monitoring and follow-up.

The question I would ask is, should there be a recommendation about how aggressively the drug is applied for lowering glycemic control. And in this sort of high-risk patient, just as for someone who has very uncontrolled blood pressure, although our goal is excellent blood pressure control, the rate to get there to protect the kidney may be a little slower, should it be the same approach with regard

to ophthalmologic complications and glycemic control and be a little bit more judicious in the rate of glycemic control? And I would assume that the answer is we don't know.

DR. WILSON: Dr. Weber?

DR. WEBER: I guess the question is it all comes down to risk-benefit. What I'm hearing from my ophthalmology colleagues to-date is that this can be managed. It can be identified and it can be managed.

Whether or not that's acceptable -- the potential risk versus the benefits that we're hearing: weight loss, glycemic control, potentially reduction in albuminuria and other outcomes -- and that's where the balance is, I think I'm hearing that this can be managed and identified, and I want to just confirm that.

DR. WILSON: Any further comments?

(No response.)

DR. WILSON: All right. We're going to try to summarize this one. The increase in absolute risk was especially noted. And those at the

highest risk and those who develop blindness especially was noted. They started out with some of the most severe complications, even noted in the chart with qualitative assessments and historic assessments in the initial evaluation.

Our ophthalmologists agreed and recommended that there be an expert ophthalmologist exam, and that would be with the visualization of the retina and that be recorded before patients start treatment.

Mostly the concern is by the non-ophthalmologists at least feeling comforted -- I think endocrinologists especially -- that an ophthalmologist can now treat these very severe problems even in the first 2 years of treatment. But perhaps we need better studies to really assess this moving forward.

I don't think I have too much more. Anything? Yes?

DR. SLEEP: Dr. Sleep. Yes, thanks. I just want a point of clarification, Mr. Chairman. Is the committee recommending routine ophthalmologic

examinations by an ophthalmologist for anyone if this drug were to be approved prior to therapy? And does that constitute a significant change in clinical practice? Why would that be required for this GLP-1 and not other agents that could potentially also lower A1c rapidly or significantly?

DR. WILSON: So the question as I understand it is what is the formal recommendation for patients who may initiate this medication? Let me first say as an endocrinologist, my best understanding is from the American Diabetes Association as an American-practicing endocrinologist that there be recently recorded, typically within 12 months, an assessment of the person's retina in the chart.

That is the standard of practice. We have some American Diabetes Association expertise in this room. And I think I'm saying that right, and they can correct me. I will recognize them if I seriously misstate that. And persons with more advanced disease, they are seen more regularly, and

we've seen slides on that today.

In fact, that is what is the expectation here in the States. I'm not sure exactly what they are outside the States. Not necessarily right at the time you initiate but within the past year, that's expected to be in the chart as a performance measure.

Does that answer your question?

DR. SLEEP: Yes, thanks. I just wanted to make sure that the labeling wouldn't require an additional assessment other than of standard of care and that labeling would potentially reflect that in those patients who have preexisting retinal disease, more frequent monitoring is required.

DR. WILSON: As you saw from one of the slides we've shown earlier today, frequency is accelerated, it goes for every quarter, for instance, for people who are already have disease or have more complications, et cetera. But for most, as was also mentioned, many, many patients have no problems, and they're on a 1 to 18 months type of return at my university and across the VA.

Do the ophthalmologists agree with what I said?

(Affirmative nods.)

DR. WILSON: Okay. Can we go on to the next item? This is E. This is in case we missed anything.

(Laughter.)

DR. WILSON: Comment on your level of concern related to the observed increased risk in diabetic retinopathy complications observed in SUSTAIN 6. Dr. Hiatt?

DR. HIATT: Just to reiterate the numbers in that trial, there were 21 excess retinopathy events, and the vast majority occurred in patients who were at high risk for such events. In the cardiovascular OUTCOME trial, though it's not inferiority, there were 138 fewer MACE events.

If you just look at that numeric difference -- and I'm not proposing that that goes any further than simply a thought experiment in this discussion -- there's a whole lot more cardiac risk avoided than retinal risk caused. My concern

about is I think it's a manageable risk that should be identified and then physicians should be aware, but it should not prevent you from using the drug.

DR. BLAHA: You said 38 MACE?

DR. HIATT: Twenty-one excess retinopathy events caused 138 MACE events avoided. But again, I'm not saying --

DR. BLAHA: I'm seeing 38.

DR. HIATT: I'm sorry. No, I did the math wrong. It's 38. I still think that you should put that in context. I don't think this is causing a huge concern.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: I don't think we should go there because we're not discussing an indication to prevent MACE, interestingly, where we could have based on the data. We consider indication to decrease blood glucose with the assumption that it will, in the long term, decrease the risk of microvascular complications, including diabetic retinopathy.

To answer the question here, my level of

concern in terms of the observed risk is moderate, but the problem is not that we'd want to avoid harm; we want benefit. We really want to reduce the long-term risk of diabetic retinopathy.

So will we observe this, and how much will it decrease risk given what we observe now? That's really a question we cannot answer based on the data, and that's a problem.

DR. WILSON: Go ahead. We have a couple more. Dr. Palevsky?

DR. PALEVSKY: Paul Palevsky. As I look at the outcomes that have the greatest concern, they are the vision loss outcomes, much less so than the interventions, photocoagulation and intravitreal injection. There, the absolute difference in numbers is very small. I think that the risk I would be most concerned about is actually a very small risk balanced against a much larger benefit in terms of the benefits associated with improved glycemic control.

While I think there needs to be a tiny bit of caution about the risk of retinopathy, worsening

of retinopathy, I think that the overall balance favors the use of the drug.

DR. WILSON: Let me also make a -- we're getting into a balance discussion, but I think my understanding of this question is, is there a greater risk in this trial than was seen in the other studies? I think that's the question, and I'm not sure how we'll answer it.

DR. SMITH: Dr. Wilson, I just want to interject.

DR. WILSON: Is that right?

DR. SMITH: No.

DR. WILSON: How do you want that?

DR. SMITH: I don't think that's really the question. We don't want cross-trial comparisons here.

DR. WILSON: Okay. What do you want?

DR. SMITH: What we're really trying to do is this is sort of a summary of A through D that you've just discussed. Perhaps you don't feel there's a whole lot that you need to summarize, but taking all these points in context, what's your

overall level of concern? We don't want really comparisons with other agents.

DR. WILSON: Thank you. Thank you very much. Dr. Ferris?

DR. FERRIS: I'd like to point out that this event calculation is not progression of retinopathy. We just heard that these people all have proliferative retinopathy that went blind and were treated. I don't think there's any evidence that says tightening blood glucose control after you have proliferative retinopathy helps your proliferative retinopathy.

You're into another mechanism of progression, VEGF-driven. And what drives retinopathy early on is different from what drives retinopathy later. So counting these events doesn't help us know whether retinopathy is going to be -- progression is going to be slowed or not, except there's such overwhelming data that lowering hemoglobin A1c lowers not just retinopathy progression but all sorts of other bad outcomes.

Finally, this difference between these, as

everybody said, we're down in the rounding there. We're talking about a 1 percent difference in a group of people that has 50 percent chance of developing retinopathy.

So I'm certainly not concerned. I think it's worth telling patients that, you need to worry about your retinopathy; I don't care what you're taking, you need to worry about your retinopathy; and maybe you need -- as we were saying like getting pregnant, if you're going to have a sudden decrease in your retinopathy, you ought to go see your eye doctor a little bit sooner.

DR. WILSON: Dr. Budnitz?

DR. BUDNITZ: Yes. I agree with folks that have already mentioned appropriate labeling based on the data, and these trials make sense, and patients and physicians should be aware of high-risk groups from this data.

My main concern is actually that we'll never know an answer and that we will have maybe increased screening. And maybe if this trial was conducted for another four years or five years,

maybe these curves will cross, and all this is about maybe no increased risk. And I don't know without further study if we'll ever know.

So I think that's a concern. We also have to think about other unintended consequences if we don't have an answer in the future about whether or not maybe there's a wholly effective glycemic control that's no different than insulin or maybe it isn't. I don't know how that will be answered in the foreseeable future.

DR. WILSON: I'm not sure how I can summarize, but we just added an extra summary statement. But I think Dr. Ferris' comment that early to moderate retinopathy is especially driven by A1c levels, very late retinopathy may be driven by fibrotic VEGF or other types of mechanisms -- and we have this issue of no matter what level in these studies, individuals who have quite different A1c drops, compared to usual care, they may progress.

For the more severe disease, we clearly need more data, especially for longer term, and what the

ramifications are for this type of medication and/or in the modern era. It's a very difficult last comment to summarize.

Any further additions, though, on that? Dr. Del Priore, we'll give you the last word if you want. You're our other ophthalmologist who's on the committee right now.

DR. DEL PRIORE: Thank you. I think that the comments, I wholeheartedly agree with two of them actually. One of them is you have to counterbalance this against the fact that there was a difference in the CVOT outcomes, that we're talking about a small percentage of patients.

I'm not alarmed to look at this question. I think if we did not have the data from the DCCT and from other trials, then this would be extremely concerning, but what we're seeing is really not inconsistent with those trials.

DR. WILSON: We have earned a break. Please come back at 15 minutes from now. We will do the final discussion question, and then we'll have a voting question. Thank you.

(Whereupon, at 3:45 p.m., a recess was taken.)

DR. WILSON: Okay. If we could take seats, we're going to get going. Question 4 is a discussion item.

"In SUSTAIN 6, a total of 254 first major adverse cardiovascular events occurred during a median two-year follow-up. The estimated hazard ratio of MACE and the components of MACE for semaglutide versus placebo are shown in the table." I'm not going to read this entire table unless I'm obligated to.

CDR BONNER: No.

DR. WILSON: Thank you, Commander LaToya. I don't have to read that. But I think you can see the top one that's highlighted in bold is the MACE and then the components of MACE.

The point is to discuss the results and comment whether these data are adequate to characterize CV safety of semaglutide. Dr. Hiatt?

DR. HIATT: Thanks. Just some thoughts about this because this I think is one of the key

reasons we're here, is to understand the cardiovascular safety of this drug. As you all know, this goes back to the 2008 guidance, which is driven by a presumed excess cardiovascular risk from rosiglitazone, which when those events were readjudicated, that risk was not well-substantiated at all.

Since then, a lot of research has been applied to this. And I think that if the drug being tested has a true hazard ratio of 1 on MACE events, that it takes a certain number of events to balance the upper bound of the 95 percent confidence interval to understand if that risk is increased or not.

My understanding of the 1.8 and 1.3 is simply a way -- the FDA should, please, comment on this -- to allow sponsors to cross 1.8 based on phase 2 data, or small phase 3 trials where the primary endpoint is A1c. And then adverse events, particularly MACE events, which hopefully are adjudicated, can round out a database with enough events to be less than 1.8. But to stay on the

market, it needs to be less than 1.3. Correct?

DR. SMITH: That's an accurate reflection of the 2008 guidance.

DR. HIATT: Okay. From my perspective, the approach is all about safety and therefore excluding risk, not about showing benefit. When you're excluding risk, you're not necessarily testing a hypothesis. You're trying to basically show that your drug is no worse than some threshold; and therefore, the more events the better, which is kind of where my question went from why the 122 initially and then the 254 at the end.

So if you look at the initial sample size estimate with a hazard ratio of 1.0, 122 events is not a lot of events. If you kind of simulate that, I would imagine that that would give you enough events to be less than 1.8.

Now, if the hazard ratio is less than 1, then that really helps you a lot because it pulls the upper bound down. So that hazard ratio with 122 events is I think around 0.70, which is

terrific because now you're actually well below 1.8. In fact, you're less than 1.3.

From a safety analysis perspective, the more events the better. So I'm really glad the sponsor went on to 254 events because your confidence that you're really below those thresholds has increased because the confidence interval simple narrow as you have more events because that hazard ratio didn't change that much, 0.70 to 0.74.

Is that right? Am I doing my numbers right?

(Affirmative nods from applicant.)

DR. HIATT: So now you're in a situation where the hazard ratio suggests a benefit, but the prespecified hypothesis is not superiority; it's not inferiority. So I think the data clearly show you beat 1.8. I also think it shows you clearly beat 1.3. When you look at that, in my mind, I think the need for additional evidence that this drug needs to rule out a cardiac safety risk is now being completely satisfied, that with an upper bound less than 1 on 254 events, it's pretty clear to me that you don't have a cardiovascular safety

risk concern.

I clearly would not go further than that because that was not the intent of the study. I would hope that clinicians reading the study or the New England Journal medicine paper would not conclude that the drug has definitively shown cardiovascular benefit because that's clearly not the intent of what the study was designed to do. But with that number of events, I think it's very clear that this drug does not carry a cardiovascular risk, safety risk at all.

So to summarize, I would give the sponsor credit for crossing both 1.8 and 1.3.

DR. WILSON: Dr. Brittain?

DR. BRITTAIN: These results are great, far exceeding the standard aimed for. I'm not sure I would be quite so fussy about saying that I wouldn't regard them as statistically superior. There are ways we can design a study for non-inferiority and still see superiority. It's all the same confidence interval. So in my view, it is superior, although again, it wasn't designed

that way.

I also think it's great because this is unlike hemoglobin A1c. This is a clinical endpoint, so it's really great that we're seeing this result. The only comment I have is that it's a little disappointing that all-cause mortality showed no indication at all of a benefit, at least at this point.

DR. WILSON: Dr. Blaha?

DR. BLAHA: Mike Blaha. I'm going to agree quite a bit with what was just said. I guess maybe just a manner of speaking, maybe we can't say it's superior, but I can say that the upper limit of the confidence interval is less than 1, which produces a statistically significant p-value. I think that's extremely relevant in this discussion.

I think if we stop at just saying, well, there's no safety hazard, then I have a harder time answering number 5 where I'm going to balance the risks and the benefits of this drug. We just had a conversation of question 3 about the retinal facts, and we're going to have to balance that with a

potential benefit in question 4 here that comes to me from the observation that the upper limit of the confidence interval is less than 1 and meets traditional, statistically significant thresholds.

I'm going to go further to 4 and say that I think while there's definitely not a safety signal, there's just no question, I don't think, anyone in this room could possibly make a comment about a safety signal when we have this data, but I'm going to go so far as saying it's extremely reassuring and potentially indicative of a benefit.

Of course, those who are cardiologists in the room see these hazard ratios, and these exceed what we've seen from a variety of other drugs added on to standard of care. And for a cardiovascular drug, this would make us jump up and down, frankly.

So it's very exciting and needs to be taken into account to a risk-benefit discussion that we'll have coming up next.

DR. HIATT: Could I just jump in clarify? The primary approval endpoint here is A1c, not MACE. So the question about risk-benefit is, has

the cardiac risk outweighed any benefit on A1c? I think you should just frame the idea that that's the primary endpoint.

DR. BLAHA: Fair. I'm going to factor that in though, I think, to my thinking about this drug, but I think that's a good point.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: It's greatly disappointing that this trial is not designed such as the LEADER trial with a longer-term follow-up and greater number of events, so that we'll really be able to answer that question that would really greatly benefit the patients, but we're not able to answer that question.

The only thing we can answer is, yes, it's definitely safe, therefore, we have to limit the approval to what the question is and not extend it to potentially weigh the benefit and risk when the trial was not designed to do so.

DR. WILSON: Dr. Neaton?

DR. NEATON: No. I think this is more than adequate to demonstrate safety. My only comment

was I thought I heard the sponsor say that the MACE outcome was consistent across the components, and I probably wouldn't have said it that way. I think this is being driven by the non-fatal outcomes in part because this is a two-year trial, likely.

DR. WILSON: Dr. Low Wang?

DR. LI-NG: I also agree that these data are adequate to characterize the CV safety of semaglutide. I also wanted to make that comment that it does look like this is driven by non-fatal MI and non-fatal stroke, not by CV death. But I'm satisfied with the safety.

DR. WILSON: Dr. Hiatt?

DR. HIATT: When I sort of looked at this, I was surprised that there wasn't that typical hierarchical testing first shown on inferiority and then move to superiority. But if you really design the trial to acquire 122 events, that would seem risky. I could sort of see why they didn't do it. We all wish they had in retrospect. I would imagine they're planning an outcome trial, but I have no idea if that's true. You guys could

comment if you want or not. But it would seem like a good place to go, so you could definitively answer the question of superiority.

DR. WILSON: Ms. Robotti?

MS. ROBOTTI: Hi. My concern is in subgroups and just that -- this may not be the right place to make this comment, so I'm just going to make it because I want to.

The trial participants are overwhelmingly white. There's just not enough subgroup participation to really do a good analysis. Cardiovascular disease is the number 1 killer of women. It's a very high killer of black people. And diabetes has a much higher incidence made in black people and in Hispanics, and they're not well-represented.

So the whole representation of subgroups and the ability to do an analysis on this concerns me. It's happened in the history of drug approvals, that after approval, information on subgroups comes out that makes it clear that that drug was very dangerous for women, or for the Hispanics, or

whatever. And I'm going to feel pretty bad if we don't go on record as saying I think that there should be more trial participants and it should reflect the group of people who would need the drug.

DR. WILSON: Dr. Hiatt?

DR. HIATT: This subgroup question came up earlier, both from some of the people commenting from the audience. And if you look at the forest plot of the MACE events, I don't see any subgroup interactions there at all. I think those p-values -- I'm not sure if you have interaction p-values. But correct, there's no interaction for gender, age, white, and U.S. non-US, right? Nothing statistically significant.

I think what you're asking is to have a larger trial where there's broader representation. But I would say, in terms of the MACE effect, I don't see anything distinguishing a particular subgroup from another in terms of responding differently compared to the overall response.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: I do share Ms. Robotti's concern, and I would share it even more if the trial was looking for an indication regarding cardiovascular events. But I think in terms of safety, even if the subgroup representation is completely inadequate, I don't think there's any signal, from the data at least that we've seen, that is a safety signal in any of those subgroups.

DR. WILSON: All right. Can I try to summarize this? Any further comments before we do that?

(No response.)

DR. WILSON: In summary for question 4, there was a very strong feeling by the committee that this was a very safe medicine in terms of cardiovascular outcomes using the MACE criteria that were employed in the trial. Particularly laudatory was the interim analysis, which showed even at the time of 122 events, they had a favorable hazard ratio.

DR. HIATT: There's no interim analysis.

DR. WILSON: I'm sorry.

DR. HIATT: There's a post hoc analysis.

DR. WILSON: A post hoc analysis --

DR. HIATT: There was an analysis done on the --

DR. WILSON: -- thank you, Dr. Hiatt -- that was imputed to the interim that showed virtually the same effect. Thank you for the clarification.

Some of the committee members felt this was close to superiority, but everybody was unanimous in supporting non-inferiority. It was felt it was unfortunate it was not a longer trial. It did not have greater representation of ethnicities and minorities, which would really help in terms of moving forward.

I think there was a sentiment not really voiced very strongly, it would be great to see a trial that might address that question. It was comforting especially to have such strong results, but, mind you, most of the results were driven by morbidity, not mortality effects.

Anything further on that?

(No response.)

DR. WILSON: Okay. All right. I think now we're ready to go to our voting question. Can we bring that up?

I'll read the question first, and then tell you how we're going to proceed. "Do the available efficacy and safety data support approval of semaglutide 0.5 mg and 1 mg administered subcutaneously once-weekly as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus?"

You have two choices, but you actually have a third. You could abstain as well. But if you vote yes, please explain your rationale and comment on whether any additional study should be required after approval. If you vote no, please describe what further studies you believe the applicant must conduct to establish a favorable benefit-risk to support approval.

Now, before we vote, for some of you who have not voted before perhaps, we're going to all vote at the same time. And when instructed by Commander Bonner here next to me, she's going to

guide us through this process. But I wanted to make a comment before she guides us through that, that each person will be asked to explain how and why you voted. So take your notes now and be ready to explain.

I won't say which direction I'm going to go. I'm going to go either this direction or I'm going to clockwise or counterclockwise, so that'll keep you all on your toes. But please be prepared to have some comments to explain. That will help us. The FDA pays tremendous attention to exactly what that discussion is related to your vote.

Can I turn that back now over to you? Is there anything further I need to make sure we say? No?

CDR BONNER: No.

DR. WILSON: Are we ready to vote? You're going to get 20 seconds to vote. And if your vote doesn't register, they'll ask us to do it again. And everybody is here in person, so we don't have any people calling in or anything as far as I know.

Yves? We have a question before we do this.

DR. ROSENBERG: I have a clarifying question. Our vote to A could be different whether or not we think that we approve it, but we do think there should be additional study performed or we just approve it? Because if we answer yes but we're not sure that any follow-up study will be done, we might change our vote. Do you see what I mean?

DR. WILSON: So he wants to vote both yes and no at the same time, I'm guessing --

(Laughter.)

DR. WILSON: -- and he wants to have explanatory commentary. This is typically what happens for -- these are tough yes/no votes because they're meant to provoke discussion afterward. And that's why the discussion is so important.

Did I answer your question? I'm not sure I did.

(Laughter.)

DR. ROSENBERG: Yes and no.

DR. WILSON: Yes and no. Does that help? Does anybody have any further need for

clarifications or can we move forward? Are we ready to go forward? All right.

(Pause.)

DR. WILSON: We need to try again. It's not anonymous for those of you who are wondering. Your name is going to be attached to this. One last time.

(Voting.)

CDR BONNER: For the record, question 5, yes, 16; no, zero; 1 abstain; no voting, zero.

DR. WILSON: Eenie, meenie miney, mo, which way should we go around as we finish? I'll start at that end.

Dr. Ferris, you're the first voting member. State your name. Each person will state his or her name and then tell us how you voted. That's also for the permanent record. We know how you voted, except for the one abstention. State your name, how you voted, and then comments please.

DR. FERRIS: This is Rick Ferris. The primary outcome was clearly met. The adverse events were mostly expected and not worrisome. I

don't know whether there's an adverse retinopathy effect or not, but it seems prudent if somebody is going to suddenly improve their blood glucose that they get regular eye exams, so I'm not worried about that. And apparently, there's some discussion about having something on the label about getting an eye exam, which is a good idea no matter what.

DR. WILSON: Thank you very much. Let's go next.

DR. PALEVSKY: Paul Palevsky. I voted yes. The benefit with regard to hemoglobin A1c was impressive. There was no cardiovascular signal for harm. The other adverse events other than retinopathy were as would be expected for this class and were not a concern. Retinopathy is, in my view, a modest concern that is outweighed by the benefit otherwise seen.

I support the sponsor's proposal for labeling similar to that for insulin. In terms of the risk of retinopathy progression, it would be very nice if we had a real retinopathy study with

documented retinal exams to resolve this question, and that would need to be a longer-term study than a two-year study.

DR. HIATT: William Hiatt. I voted yes. Just echoing the other comments, I think the primary efficacy endpoint was well-established despite the missing data issues and various way to impute it. The signal was quite strong, so it would be hard to minimize that at all. I think that's a pretty strong effect on A1c.

There were no cardiac safety concerns. I'd encourage the sponsor to carry on with a properly powered cardiovascular outcome trial with a broad representation of appropriate patients to further define the potential superiority of the drug.

In terms of the retinal findings, I think that they're likely real. I'd recommend that they be handled as a labeling issue and make the physicians aware similar to that as the label for insulin without going much beyond that. I think what physicians should do with that information is follow appropriate guidelines and things like that.

DR. YANOVSKI: Susan Yanovski. I voted yes. Glycemic control really appears to be excellent, and there were certainly no evidence of increased cardiovascular risk and, in fact, some suggestion of benefit.

In addition, the proportion of patients who achieved clinically meaningful weight loss was also impressive. Regarding the retinopathy findings, I think that monitoring the high-risk patients is important, but given effective treatments, I felt that risk is manageable. I would like to see well-designed, longer-term studies to get better data about long-term retinopathy outcomes.

DR. WILSON: Could we pause for a second? Dr. Smith, you wanted to make a comment.

DR. SMITH: Yes. I just wanted to provide a reminder, and a couple of you have done it. We might want to go back to catch Dr. Ferris' opinion. The second part, if you voted yes, which obviously 16 of you did, we would like any comment on whether any studies should be required after approval.

We will obviously have to go through the

exercise of determining whether or not we can require such studies and what those would look like. But if you feel something is very important, that it should be required, then we would want to hear that in your comments.

DR. WILSON: With that advice, why don't we circle back to Dr. Ferris and up to Dr. Yanovski. Any other comments?

DR. FERRIS: I don't think there are any other studies that are required. I would suggest an analysis that excluded all patients with proliferative retinopathy to see what that event rate looks like excluding those, because I think the lowering of hemoglobin A1c has no effect on eyes with proliferative retinopathy, and probably most of these events are coming from that group.

DR. YANOVSKI: I would think such studies are desirable, but I wouldn't think that they would need to be required.

DR. PALEVSKY: I think in the comment that I made, it would be desirable. I'm not saying that the agency should require that for labeling.

DR. HIATT: William Hiatt. No additional studies required for the labeled indication.

DR. WILSON: Why don't we proceed with Dr. Blaha? Go ahead.

DR. BLAHA: Mike Blaha. I voted yes for approval. I think there's clear evidence, as we've said, for efficacy on the HbA1c endpoint on top of diet and exercise in those with type 2 diabetes. Likewise, I'm impressed by the weight loss results, although I guess I should be reminding myself that's really not the indication. But it's extremely clinically important, that weight loss, and likely drives many of the mechanisms of benefit in the cardiovascular side.

So for the label of A1c, or the primary efficacy endpoint A1c reduction, I do believe that we've met that endpoint sufficiently.

We do have that safety signal for increased retinopathy in a trial not designed for assessing retinopathy outcome. But I'm hearing from experts, and I really appreciable my ophthalmology colleagues speaking to this, that it's not

well-designed perhaps for capturing those endpoints, so it's worth factoring in.

I'm reassured by the DCCT results and the potential mechanism that needs to be looked into further. I prefer a label consistent with that described for insulin, describing a rapid reduction of A1c and a potential risk for retinopathy and for screening. I think that sounds sufficient to me.

We do have a strong safety signal for CVOT in a fairly large study with 254 events and an upper confidence interval of 0.95 on that point estimate, which to me is a potentially clinically significant result. And while I can't say there's superiority, it's extremely important in my consideration of a compressive safety endpoint that points towards benefit more than risk for me.

Once again, my compressive assessment of the safety includes a potential benefit on cardiovascular outcomes, which to me outweighs the signal on retinopathy in this trial that was not designed to look at retinopathy.

I'd encourage my colleagues in ophthalmology

and epidemiology, whomever, to look into this idea of retinopathy as a function of A1c in the scientific community. I certainly don't think that's a requirement for the sponsor, and I don't see any further need for additional cardiovascular or other studies required for the approval of this drug.

DR. LI-NG: Melissa Li-Ng. I voted yes. I voted yes because of the data that showed sustained effective A1c lowering. Data also showed safety. And the study data also showed additional benefits such as sustained weight loss and blood pressure lowering.

The risk of worsening diabetic retinopathy seems to be manageable, and I did not think, through our discussion, that there would need to be a change in standards of care. The ADA, as Dr. Wilson had pointed, does point out ophthalmologic exams as standard of care once a year, and those are increased to every 3 to 6 months depending on the severity of retinopathy. And I do not think additional studies are required.

DR. LUMLEY: I'm Dan Lumley, patient rep from Kansas City. Next week, I have an appointment with my DO, and I plan to tell him that I was on this committee and was a voting member. And after he recovers from that shock, he will ask me -- he'll say, "Well, how did you vote, Dan?" And I'll say, "Well, after listening to the sponsors, very impressive."

From listening to 16 very knowledgeable, prestigious docs from around the country, I'm convinced that it, as everybody said repeatedly, lowers A1c, minimal cardiovascular risk, may lose weight, which most people want. The 1-week dose impressed me, lower blood pressure and tolerable side effects even though, as the report said, vomiting and diarrhea is not very exciting. But other than that, I just felt it was a definite yes. No study.

MS. ROBOTTI: I'm Suzanne Robotti, and I voted in favor of approval of the drug or advising approval. Semaglutide does show lowering of glycemic levels and body weight. It doesn't seem

to cause hypoglycemia as often as its comparator drugs.

The committee has convinced me that retinopathy is manageable and that the lack of CV harm is greater benefit. It has significant side effects and adverse events that will cause a lot of people to stop using the drug and will impinge on their quality of life.

I'm concerned about the race and ethnic make-up of the trial participants, in case you missed me saying that twice before, and the lack of subgroup analysis. Black non-Hispanics have the second highest rate of diabetes but are so underrepresented in these trials that actual black participants number in the low one hundreds, on a guess; I don't have the raw numbers.

The lack of significant subgroup analysis also concerns me. With such small samples, it's impossible to know if this drug has a differing effect and effects in safety among women or ethnic groups.

Considering the commonality of retinopathy

with diabetes, it is surprising to me that the research was not gathered in a standardized method, which made it not of the best quality. The applicant seems to be depending on other studies of other drugs to conclude that the early worsening of retinopathy shown in their trials is temporary and that there will ultimately be a benefit to the patient.

Semaglutide follows a pattern of other diabetes drugs. Continuing the study for only one year more would have confirmed a pattern similar to other drugs. But as it stands, we don't have that information. It stopped at 2 years, so we have no confirmation of any benefit, and we have risk that is not necessary to our constituency.

I strongly recommend further study that allows subgroup analysis and further tracking to find out about the long-term effect on retinopathy. I thank the committee for the robust discussion that very much informed by decisions. And I think those studies about subgroup analysis in retinopathy should be required. The public has the

right to full safety information.

DR. BRITTAIN: Erica Brittain. I voted yes. It was an uncomfortable yes because I'm worried we'll never know if this drug ultimately has the benefit on retinopathy that you would expect a highly effective glucose-lowering drug to have. So that's a little uncomfortable.

Given, as everyone has said, the dramatic results on hemoglobin A1c and cardiovascular risk on weight loss make it hard to not feel that that benefit outweighs that risk as long as it can be managed. I don't really understand about how well it can be managed. I'm trusting all of you folks on that.

As far as a future study, I potentially would love to see another study that could address the long-term risk in the high-risk population. I'm a little at a loss at what it could be since, obviously, I don't think you can do a placebo-controlled trial. Again, I can't really, at this moment, think of what a good design would be. But if you can come up with a design that

really would answer this question, I think it should be done.

DR. BUDNITZ: Dan Budnitz. I voted yes for approval because of the statistically and clinically significant reductions in A1c without evidence of significant cardiovascular harm.

There is, it seems to me, a statistical increase in retinopathy of unclear clinical significance. Despite the methodological issues, including the poorly defined or adjudicated retinopathy outcome, I think that probably biases to the null, so there's something there.

I think that statistical information that's collected should be provided to patients and prescribers ideally in terms of number needed to treat and number needed to harm for retinopathy and in particular groups.

I wouldn't want to prevent patients, particularly those at low risk without previous retinopathy, from the option of this therapy. I would not necessarily required additional studies but would hope that they are conducted. Maybe

there is a longer-term cardiovascular outcome study to demonstrate benefit that retinopathy could be included as an endpoint over the longer-term as well that progress beyond the 2 years to three, or four, or five, then that labeling could be revised with those results.

Again, it's a challenging study design, but what is the comparison group? And the question is could you use more health services research to try to answer this question with existing databases and patients that are on drugs after it comes to market? Again, I think that's a challenging issue with trying to control for the baseline risk in the population.

Again, I agree with Dr. Brittain. It's going to be hard, but would hope that maybe what happens to these patients in terms of the diabetic retinopathy could be determined. Otherwise, I think it will be a black box for the class and for the drug specifically for the foreseeable future.

DR. WILSON: Peter Wilson. I voted yes. Without repeating what others have said, I've been

thinking what might be done to improve our data and information about where we are and where we're going.

First, I echo the cardiovascular investigators. I think it would be great to have a cardiovascular outcomes trial and to show potential superiority over traditional or usual care in patients such as those who are in the SUSTAIN 6.

Remember those are 50, 60-year-old individuals with diabetes for 13 years. This is where modern-day diabetes epidemic is. For those who are familiar and not so familiar with the DCCT, that's not what the DCCT is, and the DCCT was 20 years ago. We really need more information about safety, cardiovascular safety, and then I'm really perplexed about what's going to happen in the future about eye outcomes.

I'm concerned, here we are 20 years later -- and Dr. Ferris, and Dr. Chew, and Dr. Del Priore say we're a little bit better, and now we treat but we still don't know. So that's frustrating for those of us who are metabolic

scientists.

What might be done to improve the field and our knowledge? One might be a registry for people who are fit similar to the SUSTAIN 6 entry criteria, the 50 to 60-year-old diabetics, diabetes times 10 years, and perhaps with background retinopathy. I would say not just this class of drugs, perhaps several classes of drugs.

The other thing that I would put forward -- and Dr. Ferris hinted at it -- is telemedicine. We have retinal photos for a lot of these patients across a lot of systems, and then three years later, they get photos and then try to keep track of what they were doing. Now, the trouble is they may move in and out of the medications, and that's problematic.

The other one is potentially if there is a cardiovascular outcome trial, perhaps they could insert in a three- to four-year cardiovascular outcome trial, a prospectively designed analysis that would address many of the issues that we raised today with adjudicated retinopathy. But

especially, the target would be the people with background or very mild retinopathy, whether they progress, and with a considerable metabolic component so we'd have further understanding. Thank you.

DR. ROSENBERG: It's Yves Rosenberg. I'm the lone abstention here, which shouldn't come as a surprise given my previous comments. I really wanted to vote yes, and I think there's ample reason, as others have expressed, that this drug should be approved for the indication that we saw. Rather than voting an uncomfortable yes, as Dr. Brittain expressed and because of the same concern as Ms. Robotti expressed, I wanted really to make a point to the FDA and to everybody else that there should be follow-up studies, although I was not in a position to require them. And I couldn't vote no either.

It's a tremendous lost opportunity, in fact twice lost, by first not having designed a trial with a longer enough follow-up large enough to answer the question for cardiovascular benefit,

which has a strong signal for; and second, for not doing a longer follow-up of the patients that were enrolled in this study to try to see, answer, or try address some of the concerns regarding the retinopathy.

This being said, now it's going to be much harder to do a well-designed randomized-controlled trial. As already said, what will be the control group? There's probably some innovative way with these designs that could be thought to try to answer that question, both for retinopathy and for cardiovascular outcome.

Certainly, a registry would be a first step, but I'm a little concerned that it will be hard to do because you need to have the documentation for retinopathy, and certainly, for microvascular outcomes, you need a control group. Certainly, I want to encourage both industry and FDA to work together to try to see what will be the appropriate design for a follow-up study that I really strongly hope will be done.

DR. DEL PRIORE: I'm Luciano Del Priore. I

voted yes. And actually, I voted yes even as an ophthalmologist since a lot of the concern actually is around diabetic retinopathy.

I just think that the risk-benefit ratio is extremely favorable because of the dramatic decrease in hemoglobin A1c, the weight loss numbers, and there's an excellent safety signal on the major adverse cardiac events.

The negative obviously is really what we've been talking about with the retinopathy. Ideally, I would have liked to have seen, as I'm sure everybody would have, a study designed a little bit differently. But the reality is that the adverse events that we're seeing are actually not unexpected given what we know from the DCCT.

We don't know what the 5-year or 10-year follow-up is, but I would suspect the curves will cross at some point because these patients, treated are going to have better hemoglobin A1c's, and they're just going to have less events in patients who have poorly-controlled hemoglobin A1c's.

I would like to see -- my main concern

really is about the label of this more than anything else because I think that the way patients can be harmed from this essentially is that patients are treated, and they're under ophthalmological observation and under care for ophthalmological screening.

We do have good techniques for imaging retinal pathology. We do have good techniques for treating retinal pathology, but they're only useful if the patients are being seen. So I think the label portion is actually extremely important. If that part is right, then I don't see a need for additional studies.

Of course, you can always ask for a 5- and 10-year data on this, but are we really going to learn something we don't already know because the DCCT already tells us sort of what happens at 5 and 10 years if patients are controlled better.

DR. WEBER: I'm Tom Weber, and I voted yes. I voted yes based on my overall assessment of the risk-benefit for patients with type 2 diabetes. I believe the data presented a glycemic improvement

and weight loss, which is greater than that seen with other GLP-1 analogs and which is sustainable. And the expected clinical benefits outweigh the potential risks of worsening diabetic retinopathy seen in the study.

Although there's a concern that's been raised about the risk of incomplete patient adherence to ophthalmologic follow-up and it may put them at risk for progression of diabetic retinopathy, I do not feel this potential risk outweighs the demonstrated and expected benefits of this drug.

I don't feel additional studies are needed, but I would recommend labeling on the importance of regularly scheduled ophthalmologic follow-up and the potential risk for worsening of diabetic retinopathy.

DR. LOW WANG: My name is Cecilia Low Wang, and I voted yes because I thought the available data support approval of semaglutide. I think that the efficacy data in terms of A1c lowering, body weight, durability of these effects was very

convincing as monotherapy, as well as compared to other therapies.

In terms of safety, I think that the trial, SUSTAIN 6, clearly showed cardiovascular safety. And as others have mentioned, I'm concerned about this retinopathy risk. I do think that this hazard ratio of 1.76 is concerning. It's not a hazard ratio of 1.2 or 1.3. I think it may be real.

Although retinopathy can be controlled with current treatments, right now, the current standard of care requires retinopathy screening every 1 to 2 years for most people. And it's only with insulin initiation that more frequent monitoring is done in the most recent physician statement by the ADA.

I think that one way we can get around this concern about the increased hazard ratio of retinopathy with semaglutide is specific recommendation by the FDA regarding the frequency of monitoring that's needed after this drug is initiated. I think that needs to be included in warning.

DR. EVERETT: This is Brendan --

DR. LOW WANG: I'm sorry. I'm sorry I guess I didn't mention the whole trial thing. Looking at the way this number 5 is worded, the question is whether or not any trial should be required after approval. I certainly don't think that anything needs to be required before approval and then I guess should it be required.

I would say that this level of increased risk is concerning enough to me that I would require a trial after approval, possibly either a longer study or a study that can maintain similar A1c lowering between semaglutide and an active comparator.

DR. EVERETT: This is Brendan Everett. I voted yes for many of the reasons that have been stated previously. But just to summarize them quickly, I thought the sponsor demonstrated that semaglutide could achieve the primary efficacy endpoint of hemoglobin A1c reduction with a benefit that exceeds the risk.

I thought there was clear evidence for

cardiovascular safety. And I think, as many mentioned, the data raised the hypothesis that there's actually cardiovascular benefit here, and it would be a shame not to test that hypothesis formally.

Many of the AEs that were mentioned seemed to be consistent with other agents in this drug class and may limit the ability of patients to take the drug but nonetheless are not a concern that should prevent its approval.

I think the retinopathy signal is real, as many of the others have mentioned, in spite of the issues that have been mentioned with its ascertainment and validity as a measure of clinical disease, just the way that it was ascertained.

I still think that the data that were presented earlier in this session, both from UKPDS and the ACCORD trial, and then also DCCT, are strongly supportive of the idea that long-term hemoglobin A1c reduction is good for diabetic eye disease.

We clearly don't have any data from this

session that contradicts that because we stopped follow-up in 2 years. So really what we have is an observation that is not inconsistent with prior short-term data, albeit those data collected from patients with type 1 diabetes treated with insulin 20 years ago.

I don't think that there is any need for a trial to be conducted to evaluate this adverse effect post-approval. I do think there's the opportunity to conduct a cardiovascular outcomes trial and to nest within that a small focused study of the retinopathy question. I think, again, not being an ophthalmologist and not being a statistician, but doing some clinical trials, my sense is that the number that you would need to actually enroll would be relatively small, so you wouldn't have to do the entire cardiovascular outcomes trial. The downside would be that you would have to follow them through an extended period of time on the active study drug versus potentially placebo.

With that, I'll turn it to Dr. Neaton.

DR. NEATON: Thank you. Jim Neaton. I voted yes for many of the reasons that have been stated, the cardiovascular outcome, the hemoglobin A1c, blood pressure, weight.

I actually want to congratulate the sponsor on doing well-done studies. It was very nice to see studies that were done on hemoglobin A1c where you continued to collect the data following treatment discontinuation and rescue medication, and you had 99 percent follow-up in the cardiovascular outcomes trial.

You raised a big issue for us because you collected some data on diabetic retinopathy that perhaps wasn't the best way to do it, so I'm left with this uncertain effect of how to measure retinopathy in this population, whether it's going to reverse, and also how you kind of reduce hemoglobin A1c has an impact on the initial risk in the reversal.

I do think additional research is needed, but I don't think this sponsor necessarily should be the one that does it. So I'm looking at

Dr. Yanovski and Dr. Ferris, my friend. I think you should be working with the FDA on this issue because it's broader potentially than this drug of this class. This seems like a very important issue, and I really question whether the DCCT results are relevant today.

DR. WILSON: Thank you all very much. Before we end, the FDA gets the last word here.

Dr. Smith, any last comments?

DR. SMITH: No. This has been a very helpful discussion today. We'd like to thank you all for your time, and for your efforts, and for preparing so well for this meeting. It really helps us a great deal. Thank you very much for being here.

Adjournment

DR. WILSON: All right. We stand adjourned. Be sure to take all of your belongings. Thank you. You can leave your name tags. You can leave any printed materials on the desk.

(Whereupon, at 4:53 p.m., the meeting was adjourned.)