FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEETING (EMDAC)

Tuesday, June 20, 2017

8:00 a.m. to 4:41 p.m.

FDA White Oak Campus

Building 31 Conference Center

The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction

DR. WILSON: Good morning. If we could have your attention. I would like to remind everyone to please silence your phones, take a second to do that, any other devices. And for those who may want to reach out to the FDA press contact, it's Theresa Eisenman.

Theresa, are you here? She's in the back and raised her hand.

I'm Peter Wilson. I'm the chair of the Endocrinologic and Metabolic Drugs Advisory Committee, and I'll be chairing this, this morning and this afternoon. We now are calling this meeting to order.

First, we're going to start by going around the table. And we have a few empty seats. We'll explain what'll happen with those empty seats as we go around. So let's start with the left, with the FDA.

DR. GUETTIER: My name is Jean-Marc Guettier. I'm the division director for the Division of Metabolism and Endocrinology Products.

DR. YANOFF: Lisa Yanoff, clinical team leader for the Division of Metabolism and Endocrinology Products.

DR. CONDARCO: Tania Condarco, medical officer for DMEP.

DR. GOLDEN: Good morning. Julie Golden, medical officer, Division of Metabolism and Endocrinology Products.

MS. HAMILTON: Good morning. I'm Kiya Hamilton, statistical reviewer in the Office of Biostatistics.

DR. NEATON: Jim Neaton, biostatistician, University of Minnesota.

DR. WILSON: The next several chairs are Dr. Konstam. Marvin Konstam is en route from the airport, and we expect him soon. Dr. Brendon Everett from Boston is going to be communicating by phone with us today, David Oakes by phone, Carmen Allegra by phone.

Next?

DR. ROSENBERG: Good morning. I'm Yves Rosenberg from the Nation Heart, Blood, and Lung Institute. I'm the chief of the Atherothrombotic and Coronary Artery Disease Branch in the Division of Cardiovascular Sciences. I'm a preventive medicine physician and clinical trialist.

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

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

DR. WILSON: Peter Wilson, Emory University.

DR. FRADKIN: Judy Fradkin. I'm an endocrinologist and director of the Division of Diabetes, Endocrinology, and Metabolic Diseases at NIDDK.

CAPT BUDNITZ: Dan Budnitz. I'm from the U.S. Centers for Disease Control and Prevention, Division of Healthcare Quality Promotion, and lead the medication safety Program.

DR. LOW WANG: My name is Cecilia Low Wang. I'm an endocrinologist at the University of

Colorado.

MS. HALLARE: Diana Hallare, consumer representative.

DR. CHO: Leslie Cho, cardiologist at Cleveland Clinic.

DR. BURMAN: Ken Burman, chief of endocrinology at Medstar Washington Hospital Center and a professor at Georgetown University.

DR. BLAHA: Hi. Michael Blaha, director of clinical research, Johns Hopkins Ciccarone Center for the 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.

MS. McCALL: Debra McCall, patient representative.

DR. SANOFF: Good morning. I'm Hanna Sanoff. I'm a GI medical oncologist at the University of North Carolina.

DR. ROBBINS: I'm David Robbins. I'm director of the Diabetes Institute at the

University of Kansas and a professor of medicine.

DR. WILSON: We're going to go back.

Dr. Everett, we have you by phone. Would you introduce yourself?

DR. EVERETT: Hi. Thank you. I'm sorry I couldn't be there in person. My name is Dr. Everett. I'm a cardiologist at the Brigham and Women's Hospital and Harvard Medical School, and I direct the inpatient general cardiology service there.

DR. WILSON: And the next is David Oakes. Please introduce yourself.

DR. OAKES: Hello. Yes, I'm also sorry I was unable to make in to the meeting in person. I'm a biostatistician at the University of Rochester.

DR. WILSON: And Carmen Allegra?

DR. ALLEGRA: Thank you, and good morning. My name is Carmen Allegra. I'm a medical oncologist at the University of Florida. And like the others, I'm sorry I can't be there in person.

DR. WILSON: All right.

For topics such as what we will be discussing today, there are a variety of opinions, and some are strongly held. The goal of this meeting is to be fair in an open forum for discussion of these issues and that individuals can express their views without interruption. As a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting with these guidelines.

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. 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 the meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I pass this to Commander LaToya.

Conflict of Interest Statement

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

Today's agenda involves a supplemental new

drug application for Victoza, liraglutide injection, supplemental new drug 022341, sponsored by Novo Nordisk for the proposed additional indication of as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular risk events, cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in adults with type 2 diabetes mellitus and high cardiovascular risk.

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, a conflict of interest waiver has been issued in accordance with 18 U.S.C., Section 208 B3 to Dr. Marvin Konstam.

Dr. Konstam's waiver addresses his employer's contract with a potentially competing firm regarding a potentially competing product in which the total funding is anticipated to be

between $0 and $50,000 per year. Dr. Konstam will not have any role in the conduct of the study.

The waiver also addresses a consulting agreement with a potentially competing firm regarding a potentially competing product, which he receives between $0 and $50,000 per year.

The waiver allows this individual to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/advisorycommittees/committees meetingmaterials/drugs/default.htm

Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent by fax to 301-827-9267.

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. Reshma Kewalramani is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Kewalramani's role at this meeting is to represent industry in general and not any particular company. Dr. Kewalramani is employed by Vertex 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: Thank you very much.

Dr. Konstam has now joined the meeting.

Would you introduce yourself, please?

DR. KONSTAM: Marv Konstam of Tufts Medical Center.

DR. WILSON: The next step is for Jean-Marc Guettier from the FDA -- for FDA's introductory remarks.

FDA Introductory Remarks - Jean-Marc Guettier

DR. GUETTIER: Good morning. My name is Jean-Marc Guettier, and I am the director of the Division of Metabolism and Endocrinology Products at the FDA. I would like to welcome you all to today's advisory committee meeting, which was convened to review and discuss the results of the LEADER study.

I would particularly like to acknowledge the advisors for their resilience in dealing with an unforeseen weather issue last night. Some of the advisors actually got on planes at 5 a.m., and we really appreciate the effort they made to get here or the efforts they're making to actually participate by phone today, which is a little tougher to do than in person.

Over the next 10 minutes, I will provide you with the regulatory framework for today's discussion. Some of the regulatory issues raised by this study are similar to the issues raised by another study discussed last year at another committee meeting, and some of the background material I will present may be familiar to those members who served on that committee, so bear with me.

DR. GUETTIER: First recall that antidiabetic therapies, including Victoza, are indicated as adjuncts to diet and exercise to improve glycemic control. Demonstrating an improvement in glycemic control over the median term establishes the clinical benefit of an antidiabetic drug and is used in part to support the full approval of these agents.

It's important to note that glucose lowering in the regulatory context is considered a reliable substitute for clinical benefits. The clinical benefits that follow from glucose lowering include both acute improvement in hyperglycemic symptoms

and reduction in the risk of microvascular disease complications associated with diabetes over the long term. It's also worthwhile to note that in the regulatory context, reduction in cardiovascular disease risk is not a clinical benefit attributed to glucose lowering per se because to date, no prospectively planned study has convincingly demonstrated that improving glycemic control reduces cardiovascular disease risk.

Since December 2008, FDA has recommended that applicants developing novel antidiabetic agents demonstrate that improvement in glycemic control does not come at the expense of increasing cardiovascular risk to unacceptable levels.

The LEADER study was required by the FDA to exclude the possibility that use of liraglutide to improve glycemic control in adults with type 2 diabetes increased the risk of cardiovascular disease to an unacceptably high level.

The LEADER study is the second cardiovascular outcomes trial to report on a cardiovascular benefit associated with the use of a

marketed antidiabetic. The LEADER study is also the first study to report on a reduction in cardiovascular disease risk for a marketed GLP-1 receptor agonist. The results of the LEADER study are thus a departure from previous scientific understanding and a potentially important advance for the treatment of adults with type 2 diabetes.

Today's advisory committee meeting was convened in part to discuss whether the information generated in the LEADER study provides sufficient evidence to establish that liraglutide is effective at reducing cardiovascular risk in adult patients with type 2 diabetes such that this new clinical benefit can be added to the existing U.S. product label.

Specifically, the applicant seeks to add the following claim to the Victoza label. Victoza is indicated as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events, cardiovascular death, non-fatal MI, or non-fatal stroke in adults with type 2 diabetes mellitus and high

cardiovascular risk. I'm going to ask you to keep this claim in mind in your discussions and deliberations today.

Since you will be asked to opine on whether the LEADER study results established the efficacy of Victoza for a new use, left me briefly review FDA requirements related to the evidence needed to form the basis for a new efficacy claim in the U.S.

The legal standard of effectiveness to support a new use of an approved product is described in the Federal Food, Drug, and Cosmetic Act as substantial evidence of effectiveness. In the law, substantial evidence is defined as evidence consisting of adequate and well-controlled investigations, including clinical investigations, that the drug has the effect it reports or is represented to have under the condition of use prescribed in the labeling or proposed labeling thereof.

The adequate and well-controlled statements speak to the quality of the evidence required, and this specific aspect will be reviewed in the

following slide.

With regard to the quantity of evidence necessary, the law talks about investigations in the plural form, and it has been FDA's position that Congress generally intended to require at least two adequate and well controlled studies, each convincing on its own to establish effectiveness and support approval of a new use.

The scientific basis for requiring two studies is grounded in the fact that chance, biases, biologic variability, generalizability issues, or other factors inherent to the single positive trial could lead to an erroneous conclusion that the drug is effective when in fact it is not.

Simply stated, a conclusion based on two persuasive studies will always be more secure than a conclusion based on a single comparably persuasive study. We will return to this concept in a later slide, but let me return to the issues related to the quality of the evidence required.

With regards to the quality of the evidence,

the applicant has to demonstrate that the studies were generally adequately designed and conducted. General attributes of an adequate and well controlled investigation are described in Title 21 of the Code of Federal Regulations and are summarized on this slide. I'll give you a minute to read it.

To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation related to trial planning, trial conduct, and data handling is needed. Records of this extensive documentation are submitted to the agency for review, and detailed patient records at the clinical sites are made available. You will be asked to consider the quality of the evidence generated by the LEADER study in your discussion this afternoon.

Let me return to issues surrounding the quantity of evidence necessary to support a new claim. Although, as stated earlier, two adequate and well controlled studies are generally needed to form the basis of an effectiveness claim, the FDA

has recognized that there are certain circumstances when a single study could constitute substantial evidence.

In 1997, the Federal Food, Drug, and Cosmetic Act was amended to make it clear that the agency could consider data from one adequate and well-controlled clinical investigation, and confirmatory evidence to constitute substantial evidence, if the FDA determines that such data and confirmatory evidence are sufficient to establish effectiveness. And indeed, FDA has at times relied on a single adequate and well-controlled efficacy study to support approval of a new drug or a new use. This has generally occurred only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit.

Whether to rely on a single adequate and well-controlled study to form the basis of a new claim is inevitably a matter of judgement, and as stated previously, a conclusion based on two persuasive studies will always be more secure than

a conclusion based on a single persuasive study.

The agency's view on when a single trial could serve as the basis to conclude that substantial evidence has been met is described in guidance. In this document, the agency provides examples of some of the characteristics of a single adequate and well-controlled study that can be considered when deciding whether the single study could potentially form the basis of a new efficacy claim. These characteristics are shown on the slide.

Although the list is not exhaustive and no one single characteristic is necessarily determinative, the presence of one or more of these in a study may provide support to reach a conclusion that reliance on a single study is appropriate.

In your discussion this afternoon, we will ask you to consider whether the characteristics of the LEADER study are such that reliance on a single study to establish the new benefit of a drug is appropriate.

Having reviewed the expectations regarding the quality and the quantity of evidence needed to form the basis of a new claim, let me describe your charge today. The committee was convened to review the evidence generated in the LEADER study. After reviewing the evidence, we will ask you to advise the agency on two issues.

The first will be focused on findings related to specific non-cardiovascular safety outcomes of interest collected in LEADER. The second issue will focus on whether the LEADER study provides the substantial evidence required to form the basis of a new claim.

Let me turn to the specific discussion points and voting questions.

As just stated, the first discussion point focuses on non-cardiovascular safety outcomes collected in LEADER. You will hear today why certain specific non-CV safety outcomes were of interest and were prospectively collected in LEADER.

In this discussion point, we would like to

hear your opinion on whether LEADER further informs the existence of a potential causal relationship between use of liraglutide and one or more of these outcomes.

Although we recognize that for some of you these outcomes may be from disease areas outside of your immediate field of clinical expertise, the discussion point focuses on the existence of a potential causal relationship. We therefore expect broad participation from members in this discussion point.

The second discussion point focuses on the cardiovascular outcomes findings in LEADER and is divided into two sections. In the first section, we ask you to opine on whether the evidence generated by LEADER adequately addresses the post-approval CV risk assessment as recommended in the 2008 FDA guidance titled, Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.

In the second section, we ask you to opine on whether the evidence generated by the LEADER

study is persuasive enough to establish that liraglutide reduces the risk of major adverse cardiovascular events in adults with type 2 diabetes and high cardiovascular risk. In this discussion, we ask you to consider several the factors listed.

After the discussion, we will ask you to vote on two questions. We will first ask you to vote on the following.

Do the results of LEADER establish that use of liraglutide in patients with type 2 diabetes mellitus is not associated with unacceptably high cardiovascular risk? Please answer yes or no, and provide the rational for you response after the vote for the record.

In the second voting question we ask, does the LEADER trial provide the substantial evidence needed to establish that liraglutide 1.8 milligrams daily reduces cardiovascular risk in patients with type 2 diabetes?

Again, we will be very interested in hearing the rational that informed your vote. If you vote

yes, we would like you to describe the population for whom you believe this benefit applies. If you vote no, we would like you to comment on what additional data would be needed.

Thank you very much. That concludes my introductory talk.

DR. WILSON: Thank you very much. Before we go to the next segment, Dr. Kewalramani has joined. Would you introduce yourself by phone?

DR. KEWALRAMANI: Yes. Thank you. This is Reshma Kewalramani. I'm the industry representative, and I head up late development at Vertex.

DR. WILSON: Thank you very much.

The next segment will be the presentations by the applicant, and we have some introductory remarks related to that.

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

an individual's presentation.

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

Applicant Presentation - Robert Clark

MR. CLARK: Mr. Chairman, members of the committee, FDA colleagues, good morning. I'm Robert Clark, vice president of regulatory affairs

at Novo Nordisk. We're pleased to be here today to present data from the dedicated cardiovascular outcomes trial known as LEADER, and we're presenting these data to support a new indication for liraglutide.

Liraglutide is a long-acting glucagon-like peptide-1 and GLP-1 receptor agonist. Over the past seven years, liraglutide has become the most prescribed GLP-1 receptor agonist in the world. Throughout the presentation today, we'll use liraglutide to refer to the marketed product Victoza at doses of 1.2 and 1.8 milligram daily for diabetes.

Victoza is currently approved in more than 100 countries. It obtained marketing authorization in the European Union in 2009 and FDA approval in 2010. The original liraglutide phase 3a clinical program evaluated over 6800 patients with type 2 diabetes across a variety of pivotal study designs.

Since its approval, liraglutide has accumulated more than 6 million patient-years of experience. Its extensive postmarketing data has

reaffirmed liraglutide's effectiveness and safety profile in real-world clinical practice, substantiating its favorable benefit-risk ratio. Additionally, a higher dose of liraglutide of 3 milligrams per day is approved for weight management under the trade name, Saxenda.

Liraglutide is an analog of human glucagon-like peptide-1 with 97 percent homology to human GLP-1. Its mechanism of action depends upon activation of a highly specific cell service receptor with well-characterized cellular and organ distribution.

GLP-1 is a physiological regulator of blood glucose and body weight, and liraglutide harnesses these well-described actions. Furthermore, the scientific literature hypothesizes an independent effect of liraglutide on atherosclerosis.

Establishing cardiovascular safety of new medicines intended to treat type 2 diabetes is an important undertaking. We submitted the original liraglutide NDA prior to the 2008 FDA guidance requiring pre-approval evidence of cardiovascular

safety for new drugs to treat type 2 diabetes.

A post hoc meta-analysis of data from our phase 3 program did not suggest cardiovascular harm. The hazard ratio for time to first MACE was 0.73 with an upper bound of the 95 percent confidence interval of 1.41, which was above the 1.3 upper bound recommended by the FDA guidance to show acceptable CV safety.

As part of our postmarketing requirement to establish the CV safety of liraglutide, Novo Nordisk conducted a large randomized cardiovascular outcomes trial using a 3-component endpoint of major cardiovascular events, or MACE, as the primary outcome.

The LEADER trial followed a prespecified analysis plan driven by three main goals; first, to assess CV safety by establishing non-inferiority with a margin of 1.3. To accurately assess CV safety in LEADER, we needed to enrich the number of cardiovascular events. We therefore enrolled patients with high CV risk and required at least 611 first MACE to meet our primary objectives.

The second goal was to test for CV benefit by establishing superiority. And finally, to gather long-term data on medical events of special interest, or MESIs, all patients have a treatment period of at least 42 months. As such, the study was both event-driven and time-driven.

LEADER provides an important opportunity to augment our knowledge of the benefit-risk profile of liraglutide. Today we'll review with you the data from the LEADER trial, which demonstrate that liraglutide provides a clinically meaningful and consistent cardiovascular benefit for patients with type 2 diabetes at high cardiovascular risk.

Not only did liraglutide rule out cardiovascular harm with an upper bound of the two-sided 95 percent confidence interval below 1.3, it achieved a statistically significant and clinically meaningful 13 percent reduction in time to first MACE with the upper bound of the 95 percent confidence interval below 1. This reduction in MACE included a 22 percent reduction in cardiovascular death for patients receiving

liraglutide. In addition, the data reaffirmed the established safety profile of liraglutide.

In total, the LEADER study reinforces the favorable benefit-risk ratio of liraglutide for use in patients with type 2 diabetes, a use which is also supported by recent medical guidelines.

Based on the results of LEADER and another cardiovascular trial with empagliflozin, the American Diabetes Association now recommends empagliflozin or liraglutide as standard of care in patients with type 2 diabetes and established cardiovascular disease. The ADA has made this recommendation because both medicines have been shown to reduce the risk of cardiovascular mortality, as well as all-cause mortality.

Here's the currently approved indication for Victoza: to improve glycemic control in adults with type 2 diabetes. Based on the cardiovascular benefits observed in LEADER, we're seeking an additional indication that will expand our label to include cardiovascular protection.

Specifically, liraglutide will be indicated

as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes at high cardiovascular risk.

Let me review the remaining agenda for this morning. Dr. Steve Marso, a cardiologist from HCA Midwest Health Heart and Vascular Institute with expertise in the design and conduct of cardiovascular outcome trials, will discuss the clinical design of the LEADER trial. Dr. Marso was co-chair of the steering committee for LEADER.

Dr. Alan Moses, global chief medical officer from Novo Nordisk, will then present the cardiovascular outcome results.

Next, Dr. Todd Hobbs, the U.S. chief medical officer from Novo Nordisk, will review the clinical safety data. Then, Dr. John Buse, an internationally recognized endocrinologist from the University of North Carolina and co-chair of the steering committee for LEADER, will discuss the clinical implications for this new indication. Finally, Dr. Moses will return to conclude and

answer any questions.

We're also joined today by Dr. Anil Rustgi, division chief of gastroenterology from the University of Pennsylvania, and Dr. Janet Wittes, who is the president of Statistics Collaborative Inc. All of our external experts or their institutions have been compensated for their time and travel expenses.

I will now invite Dr. Marso to the podium.

Applicant Presentation – Steve Marso

DR. MARSO: Thank you, and good morning. I'm pleased to be here. My name is Steve Marso, and I'm a clinical cardiologist and clinical investigator. Along with Dr. John Buse, I served as co-chair of the LEADER steering committee and helped to design, oversee, execute, and report this clinical trial.

Let me walk you through the LEADER design. LEADER was a global, randomized, double-blind, placebo-controlled trial designed to assess the effect of liraglutide on cardiovascular outcome and long-term safety in adults with type 2 diabetes and

at high risk for cardiovascular events.

All potential participants underwent a run-in phase with placebo injections prior to randomization to assure that they could adhere to the subcutaneous route of study drug administration. Patients were then randomized 1 to 1 either to liraglutide 1.8 milligrams per day or a matching placebo injection, both on a background of standard of care.

The initial dose of liraglutide or placebo was 0.6 milligrams per day and was escalated weekly to achieve the target dose of 1.8 milligrams per day, according to the current label. This trial was both event and time-driven. The minimum number of first MACE was 611 and the minimum observation duration was 42 months in order to adequately evaluate long-term safety.

Vary specific efforts were undertaken to ensure that patient retention would be high, and to limit missing data. At the end of the treatment period, patients were followed for 30 days off study medication for additional safety monitoring.

The American Heart Association, the American Diabetes Association, the European Society of Cardiology, and the European Association for the Study of Diabetes have published guidelines using a multifactorial approach as shown.

LEADER followed these guidelines for standard of care. Each risk factor was addressed with specific recommendations to investigators. We used a proactive, global strategy to communicate those recommendations to trial leaders, investigators, and sites. This was the cornerstone of our strategy to establish the optimal background therapy for all patients in this trial.

I will now review the inclusion criteria. All enrolled patients had a diagnosis of type 2 diabetes and a baseline hemoglobin A1c of 7 percent of greater. There was no upper limit to the level of hemoglobin A1c at baseline.

In order to accrue an adequate number of cardiovascular events, we applied an enrichment strategy using the inclusion criteria shown here. The two sets of criteria 3a and 3b do not represent

classic primary and secondary prevention; rather, they represent a continuum of cardiovascular risk.

You'll see shortly that this strategy was effective. We enrolled a high cardiovascular risk population who experienced a greater number of observed cardiovascular events than we initially expected.

Turning to the endpoints, the primary endpoint for this trial was the time to the first 3-component MACE consisting of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The endpoint was evaluated using the full analysis set of all randomized patients according to an intention-to-treat principle comparing liraglutide to placebo.

LEADER also included secondary endpoints. These consisted of a 6-component expanded MACE comprising the 3-component MACE along with hospitalization for heart failure, hospitalization for unstable angina, and coronary revascularization. This endpoint was evaluated as a composite and by the individual components.

All-cause mortality, microvascular events, and hemoglobin A1c were other key secondary endpoints.

This slide shows how events were selected for the analysis of MACE. This is a theoretical patient who experiences each of the 3 events that comprised the primary endpoint: first, a non-fatal myocardial infarction; second, a non-fatal stroke; and lastly, death from cardiovascular cause.

For the primary endpoint, the non-fatal myocardial infarction was included in the primary analysis of time to first MACE. The other events, non-fatal stroke and CV death, were not included in the primary analysis.

For the time to first event analysis for the individual components of MACE, the first event went into the time to first non-fatal MI. The second and third events only contributed to the analysis of time to first non-fatal stroke and time to CV death, respectively. The sum of the events in the individual components of MACE was therefore not equal to the number of first events and the primary composite endpoint.

Before we review data, it is important to understand the structure of oversight for this trial. A blinded expert steering committee, co-chaired by Dr. John Buse and myself, was responsible for designing the protocol and providing scientific leadership for the trial.

The committee consisted of global academic experts with experience in conducting cardiovascular outcome trials and extensive clinical experience in relevant medical specialties. There were 18 members; four of these were employees of the sponsor Novo Nordisk.

In addition, an independent external data monitoring committee performed ongoing evaluation of unblinded safety data from the clinical trial. An independent event adjudication committee blinded to treatment assignment was formed to perform adjudication of the primary endpoint plus additional predefined endpoints of interest.

There were five predefined ways to trigger events for adjudication. First, investigators were instructed to send all deaths and medical events of

special interest for adjudication.

Second, ECGs were systematically collected and were sent for central reading by a board certified cardiologist. ECGs suggestive of new ischemia were then sent for adjudication.

Third, out-of-range lab values could also be sent for adjudication. Fourth, the event adjudication committee or contract research organization could identify new events relevant for adjudication during review of source documents submitted for another adverse event.

Finally, the sponsor preformed predefined MedDRA searches on all reported adverse events to identify potential events to be sent for adjudication.

All data were gathered by an independent contract research organization that prepared documentation prior to distributing these cases to the adjudication committee.

The EAC comprised 4 specialized subcommittees with 19 active members who are board certified clinical experts in the diagnosis and

treatment of the different endpoints and medical aspects of clinical trials. Each event sent for adjudication was evaluated independently by two primary adjudicators of the appropriate specialty using predefined definitions and guidelines.

If the two adjudicators could not reach agreement, the event was then sent to the EAC chair. The chair then preformed an independent review of all data associated with that event, including the primary adjudicator's assessment before making a final determination.

A cardiovascular subcommittee adjudicated cardiovascular events and all deaths regardless of cause. The other three subcommittees adjudicated nephropathy and retinopathy events, pancreatitis events, and neoplasms, including thyroid neoplasms.

Moving now to our statistical analysis, the objective of LEADER was first to test for non-inferiority of the primary MACE endpoint by demonstrating an upper bound of the two-sided confidence interval of less than 1.3.

If non-inferiority was confirmed, thus

establishing the CV safety of liraglutide, superiority of liraglutide over placebo would be tested and confirmed if the upper bound of the two-sided confidence interval was less than 1.

In addition to the primary analysis using the full analysis set, we defined several different analyses to test for consistency. These included a per-protocol population, which included all patients who took at least one dose of trial drug and had no more than 120 cumulative days off of study medication. Next, the on-treatment analysis included all patients, but only those events that occurred while the patient was on study medication.

Finally, the on-treatment plus 30-day analysis included events while patients were on treatment, plus events within 30 days off study medication.

In addition to the analysis just mentioned, we predefined completers as patients who either had a primary endpoint, died due to non-cardiovascular causes, or had direct contact with study staff at or after the last planned follow-up visit.

With this definition in mind, I will review the patient disposition of LEADER. An important element of LEADER was the high completion rate and small amount of missing data. 9,340 patients were randomized and represent the full analysis set. Approximately 97 percent of the population were completers as I just defined. Only 29 patients had an unknown vital status at the end of the trial.

In summary, LEADER was a trial with a relevant, high-risk, diabetes population designed to address both CV safety and efficacy. The trial had structured external oversight with an experienced steering committee and an independent external safety monitoring committee.

Finally, the small amount of missing data speaks to the robustness of the LEADER design and execution. Thank you, and with that I'll turn to Dr. Moses to discuss the efficacy results.

Applicant Presentation - Alan Moses

DR. MOSES: Thank you Dr. Marso.

I'm Dr. Alan Moses, global chief medical officer at Novo Nordisk. I'm very pleased to

present the results for the LEADER cardiovascular outcomes trial.

As you will see, the five-year LEADER cardiovascular outcome trial with liraglutide in type 2 diabetes patients at high cardiovascular risk established cardiovascular safety by excluding a non-inferiority margin of 1.3.

LEADER also established superiority for the cardiovascular endpoints by demonstrating statistically significant and clinically meaningful reductions in the primary endpoint of 3-component MACE. Expanded MACE, and all-cause mortality were also improved. Additionally, we observed consistent effects across all cardiovascular components.

These reductions were achieved in nearly all prespecified subgroups and provide substantial evidence to support the superiority of liraglutide versus standard of care.

I'll begin with some demographic data. Overall, baseline demographics were balanced between groups. The mean age was 64 years with

more than 800 patients over the age of 75. Around 65 percent of the population was male, and the racial distribution was representative of the countries in which the study was conducted. The mean BMI was 32.5 and in the obese range. Approximately 65 percent of individuals were recruited from the United States, Canada, or Europe. The average hemoglobin A1c at entry was high at 8.7 percent, and patients self-reported having diabetes for mean of more than 12 years.

In LEADER, 80 percent of enrolled patients in both treatment arms were enrolled based on inclusion criteria 3a of established cardiovascular or chronic kidney disease and represented those at highest risk in the study. Overall, these patients were older, had longer diabetes duration, worse glycemic controlled, and more comorbid conditions than those in the phase 3 trials.

Moving to baseline cardiovascular risks, the cardiovascular profiles were balanced between liraglutide and placebo arms. Up to 39 percent of patients had a history of at least one prior

cardiovascular event, arterial revascularization, or arterial stenosis; 14 percent had evidence of chronic heart failure, New York Heart Association class 2 or 3; 25 percent had evidence of chronic kidney disease.

We also looked at baseline renal status by degrees of renal impairment. Approximately 20 percent, representing nearly 2,000 patients, had moderate renal impairment with an eGFR of less than 60, and 224 patients were classified as having severe renal impairment with an eGFR of less than 30.

Now let's look at observation time and exposure to study drug. The median observation time of the trial was 3.8 years. Observation time is defined as duration in the trial, including periods off treatment with trial drug. Exposure time is defined as duration of the trial on treatment with trial drug.

The median drug exposure time was 3.5 years corresponding to more than 14,000 patient-years of drug exposure in each arm. More than 70 percent of

patients were on therapy for greater than 3 years. Almost 20 percent of patients were exposed to study drug beyond 4 years.

Now, let's turn to the MACE results. Based on a higher than expected event rate, LEADER recruited 1302 first MACE events. Over the duration of the trial, 608 or 13 percent of liraglutide treated patients experienced a first MACE compared to 694 or 14.9 percent of patients in the placebo arm, representing and absolute reduction of 1.9 percent.

All three components of MACE contributed to the risk reduction observed with liraglutide, cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

LEADER met its prespecified primary endpoint of demonstrating non-inferiority for time to first 3-component MACE. The hazard ratio was 0.87 with a 95 percent confidence interval of 0.78 and 0.97.

The p-value for non-inferiority, demonstrating cardiovascular safety, was statistically significant at less than 0.001 with

an upper bound below 1.3 and indeed below 1.0.

The trial also provided substantial evidence of cardiovascular protection through prespecified superiority testing with a statistically significant p-value of less than 0.005.

Let's look more closely at each of the components of the primary endpoint. Liraglutide reduced cardiovascular death with a hazard ratio of 0.78 and an upper 95 percent confidence interval below 1.0. This represents a 22 percent reduction in risk compared to placebo.

Both non-fatal myocardial infarction and non-fatal stroke results are supportive with point estimates below 1, but with confidence intervals spanning 1.

The analyses you see for the individual MACE components are based on time to first event for each component. Thus, the sum of the individual components exceeds the number of events in the primary composite endpoint.

Although the study was powered for the composite MACE endpoint and not to evaluate each

component individually, the consistent findings of hazard ratios less than 1 for each of the three components supports the primary endpoint.

In all cases, patients taking liraglutide in addition to standard of care had a reduction in the number of cardiovascular events compared to placebo.

We conducted several prespecified sensitivity analyses to test the validity of the primary analysis. All analyses, including per protocol, on treatment, on treatment plus 30 days, adjusting for multiple covariates, adjusting for country effect, and stratified by severe renal impairment confirmed the primary endpoint with very similar hazard ratios and all confidence intervals below 1.0.

The lowest hazard ratios were seen in the on-treatment analyses. These analyses reinforced the robustness of the primary analysis, and further support the clinical benefit of liraglutide in the high-risk diabetes population enrolled.

LEADER was characterized by very little

missing data. Only 29 patients of 9,340 had missing vital status at the end of trial. Nevertheless, we undertook two post hoc tipping point analyses to evaluate the potential impact of missing data on the result of the primary analysis.

In the first analysis, the 12 patients in the liraglutide group with unknown vital status at follow-up were added in a stepwise fashion under the assumption that they died from cardiovascular causes the day after last contact. In contrast, the 17 missing patients in the placebo arm were assumed to be alive. This is a worst-case model. The results of this analysis continued to favor liraglutide.

In the second analysis, all non-completers in the liraglutide group were added in a stepwise fashion under the assumption that they had a non-fatal MI or non-fatal stroke the day after the last contact. In this analysis, 21 of the 139 non-completing patients in the liraglutide group would need to have experienced an event versus none of the 159 non-completing patients in the placebo

group before superiority was lost.

These scenarios are highly inconsistent with the reporting of events observed in both treatment groups; therefore, both are unlikely. Thus, the tipping point analyses further support the robustness of the results for the primary endpoint.

Now let's consider the secondary outcome studied. We saw a clinically meaningful reduction in the expanded 6-component MACE endpoint, which accumulated a total of 2,010 first events. The hazard ratio was 0.88 with the upper bound of the confidence interval below 1, indicating a 12 percent reduction in risk.

The broadened composite endpoint provides additional assurance about the overall CV benefit from liraglutide when added to standard of care. Beyond the composite endpoint, it also was informative to evaluate each of the individual components of the expanded MACE. Not only are the strict first MACE and expanded first MACE aligned, an analysis of events for each of the components supports the primary endpoint analysis.

We've already reviewed the three components of the primary endpoint, that is CV death, non-fatal myocardial infarction, and non-fatal stroke. The additional components, unstable angina leading to hospitalization, coronary revascularization, and hospitalization for heart failure, provide directionally supportive results with point estimates all below 1.

The total number of cardiovascular events for each component was less in liraglutide treated patients. These findings demonstrate that the composite endpoint results are robust and support the cardiovascular benefit of liraglutide.

Now let's look at prespecified subgroups. Results for key demographic subgroups support the MACE primary endpoint. Recognizing that some subgroups are relatively small, the results are nonetheless reassuring with consistent findings by gender, age, or race.

The only demographic that did not show a numerical advantage for liraglutide was North America. This difference did not achieve

statistical significance for interaction, but did prompt an extensive evaluation of covariates though a series of post hoc analyses.

Here's a list of the covariate categories that we specifically studied for the U.S. population, which represented 88 percent of the North American cohort. None of these explain the differences in time to first MACE between the U.S. subgroup analysis and the primary analysis.

We applied an on-treatment sensitivity analysis to the U.S. population just as we had to the full data set. The primary analysis is shown at the top. Next plotted is MACE for the U.S. population, which was very similar to the total North American population that we've just seen.

The on treatment and on treatment plus 30 days analyses provided hazard ratios less than 1 and similar to the hazard ratio of the primary analysis. These results suggest that the U.S. population is not different from the overall population when individuals are taking study drug.

Let's return to the prespecified subgroup

analyses in the overall population. Subgroups characterized by BMI, glycemic control at baseline, diabetes duration, and renal function all had point estimates for time to first MACE below 1.0. All baseline renal function subgroups demonstrated favorable point estimates.

One of the two subgroups based on the cardiovascular inclusion criteria had a hazard ratio greater than 1, as shown at the bottom of the slide. The inclusion criteria 3b group had less advanced disease as we defined earlier. And as predicted, the number of events in this group was low, contributing only 10 percent of the total events in the study. This resulted in a wise confidence interval spanning 1. Thus, the apparent difference between this group and the overall population likely is the consequence of the small number of events in this group, as often seen in subgroup analyses.

To better understand the generalizability of the reduction in CV events, we conducted a post hoc analysis by taking individuals who had no history

of a previous MI or stroke and those with a prior history of these events. This is analogous to evaluating primary and secondary prevention.

Let's first look at a subgroup of 3,692 patients who had had a prior history of MACE. Here, liraglutide reduced time to first MACE with a hazard ratio of 0.84. When we assessed patients with no prior event, who numbered more than 5600, we saw a similar trend relative to placebo and a hazard ratio less than 1. This analysis further supports the primary analysis and suggests that liraglutide is effective across the continuum of CV risk in type 2 diabetes.

Now let's turn to all-cause mortality. All-cause mortality was an important secondary endpoint. The hazard ratio for all-cause mortality was 0.85 with an upper bound of the confidence interval of 0.97. We see a consistent and clinically meaningful reduction in the number of deaths among patients treated with liraglutide. This was driven by the previously mentioned 22 percent reduction in cardiovascular death.

The Kaplan-Meier plot for all-cause mortality displays a profile similar to that for the composite first MACE. The decrease in cardiovascular events, including cardiovascular mortality, was accompanied by a clinically meaningful reduction in all-cause mortality. These data underscored the clinical benefit of liraglutide in this type 2 diabetes population.

Here, we see the Kaplan-Meier plot for non-cardiovascular death. As you can see, both placebo and liraglutide had comparable non-cardiovascular related death events over time.

LEADER also evaluated microvascular complications associated with long-standing diabetes. A secondary objective was to evaluate the effects of liraglutide on a composited microvascular event. The prespecified endpoints included composites specific for nephropathy and for retinopathy endpoints, including each of the individual components.

Both nephropathy events and retinopathy events were defined as medical events of special

interest and were therefore required to be reported by investigators. However, whereas the nephropathy events were readily identifiable based on preplanned laboratory evaluations and hard clinical outcomes, the identification of the retinopathy events was limited by a lack of systematic or standardized retinal exams in the study.

There was a lack of consistency among the components of the composite raising questions about the clinical validity of this overall microvascular composite.

There was a strong trend toward improvement and persistent microalbuminuria, which contributed about half of the events. There was no improvement in the retinopathy composite or its components.

Moving to glycemic efficacy, although change in hemoglobin A1c was not the primary outcome in LEADER, it is important to consider A1c when looking at any trial in patients with diabetes. In both treatment groups, investigators were to employ standard care for diabetes. Intensifying medical therapy is needed to achieve a target A1c value

below 7 percent.

As expected, based on prior diabetes trials and real-world clinical experience, liraglutide provided substantial and sustained reductions in hemoglobin A1c when added to standard of care that were greater than standard of care alone. The decline of hemoglobin A1c was rapid achieving its maximal effect by 3 months.

Unique to the CV EOT is the fact that there was no upper limit to baseline hemoglobin A1c resulting in a mean entry A1c of 8.7 percent. Liraglutide patients were more likely to reach their blood glucose targets while at the same time less likely to require the addition of other diabetes medications to improve glucose control than patients in the placebo arm.

By the end of the trial, approximately 45 percent of patients in the placebo arm, here shown in light gray, and substantially more than the liraglutide arm, shown in dark blue, underwent some intensification of diabetes treatment usually with the addition of insulin. As seen on the

slide, the difference favored liraglutide with a hazard ratio of 0.64 and a narrow confidence interval.

Let me summarize the overall efficacy findings. The extensive data for LEADER demonstrate that over a period of 3 and a half to 5 years, liraglutide does more than improve glucose control. It provides robust and consistent benefit for long-term cardiovascular outcomes.

Superiority of liraglutide over placebo was confirmed for time to first MACE. The risk of MACE was significantly reduced by 13 percent, and expanded MACE was reduced by 12 percent. The result was consistent across sensitivity analyses.

Each of the 3-MACE components and the primary endpoint also showed consistent results with all point estimates below 1, favoring liraglutide. This also was true of the three additional components in the expanded MACE. Importantly, cardiovascular mortality was reduced by 22 percent.

Finally, liraglutide was associated with a

clinically meaningful 15 percent reduction in all-cause mortality. The data support the use of liraglutide to treat patients with type 2 diabetes and high cardiovascular risk to improve glucose control while affording protection against major cardiovascular events.

I'd like to invite Dr. Todd Hobbs to the microphone to present the safety findings.

Applicant Presentation - Todd Hobbs

DR. HOBBS: Good morning. My name is Todd Hobbs, and I am the U.S. chief medical officer at Novo Nordisk. I'll now review with you the general safety data from the LEADER trial.

As mentioned earlier, LEADER was designed to evaluate two safety areas. The first was an assessment of cardiovascular safety. The second purpose for LEADER was to further assess the long-term safety of liraglutide by collecting data for a number of medical events of special interest.

Five-year safety data from the LEADER trial in more than 9,000 patients with type 2 diabetes and high cardiovascular risk reinforces the known

liraglutide safety profile. This safety profile was first established with the extensive diabetes and weight management clinical development programs, along with now more than seven years of postmarketing experience.

In addition, the LEADER data provide considerable reassurance with regard to the potential safety concerns that were investigated at the time of the diabetes approval, including thyroid carcinomas, other neoplasms, and pancreatitis. LEADER's safety data also support the current product labeling to address the potential risks for patients who use liraglutide.

Let's first review how the safety data were collected. LEADER incorporated a targeted approach to safety data collection. Investigators were specifically instructed to report serious adverse events and medical events of special interest that are listed here. These events are either common to GLP-1 receptor agonists previously identified in the liraglutide development programs or general events of interest for diabetes therapies.

In addition to SAE and MESIs reporting, investigators could report any adverse event that they suspected to be related to trial product. This is the typical method of adverse event collection in a post-approval cardiovascular outcomes trial.

As shown at the top of this slide, all cardiovascular, microvascular, neoplasm, or pancreatitis events were identified by the adjudication process. Other event types were identified through MedDRA searches, information on the electronic data capture forms, or from laboratory measurements.

In this presentation, I will focus on the medical events of special interest highlighted in blue here. Among the most common SAEs or non-serious MESIs reported in LEADER were cardiac disorders. In line with the primary MACE analysis, cardiac adverse events were reported less frequently in the liraglutide group compared to placebo. Consistent with the known safety profile for GLP-1 agents, events of nausea occurred more

frequently in the liraglutide group compared to the placebo group.

Looking now at adverse events leading to discontinuation of treatment, more patients on liraglutide permanently discontinued treatment due to a serious adverse event or non-serious MESI than those on placebo, 9.6 percent versus 7.3 percent. The discontinuations due to an SAE or those classified as severe by the investigator were similar between liraglutide and placebo.

The difference in treatment discontinuation between liraglutide and placebo was mainly attributable to a higher incidence of the gastrointestinal events such as nausea, vomiting, and diarrhea, consistent with the known adverse event profile of GLP-1 agents. Other adverse events leading to permanent treatment discontinuation were of low frequency and balanced between the two treatment arms.

Let me now review key safety areas of interest from the LEADER trial. These include events of acute gallbladder disease, pancreatitis,

neoplasms, and hypoglycemia. The LEADER data provides substantial support for the long-term safety for liraglutide. With the exception of gallbladder events, these areas were generally well-balanced and were consistent with the established safety profile for liraglutide.

In LEADER, there was an imbalance in the number of acute gallbladder events reported. The imbalance was mainly attributable to events of cholelithiasis and acute cholecystitis, which both occurred more frequently in the liraglutide group compared to the placebo.

Based on similar findings from the liraglutide weight management program, the increased risk of gallbladder disorders is currently addressed in the adverse reaction section of the liraglutide labeling. The findings from LEADER are consistent with the current label language.

Moving to pancreatitis, in reviewing both acute and chronic pancreatitis, there was no increase in confirmed events for liraglutide versus

placebo in LEADER. Nineteen events were confirmed by adjudication in the liraglutide group and 33 in the placebo arm, with the majority of acute pancreatitis events classified as mild in severity. This is an important finding since pancreatitis is currently an area of special interest for incretin therapies.

As the LEADER trial was a large, double-blind, long-term safety study, these results are reassuring in regards to the risk of pancreatitis when compared to standard of care in patients with type 2 diabetes.

Moving now to neoplasms, during the LEADER trial, all events suggestive of a neoplasm were reviewed independently in a blinded manor by two primary adjudicators within the neoplasm subcommittee. The committee reviewed all available source documentation including laboratory results, imaging, and histopathology in order to confirm a neoplasm event.

The overall incidences of neoplasms were similar between liraglutide and placebo. However,

when looking across tissue types, we see there are slight numerical imbalances in both groups, some favoring liraglutide and others favoring placebo. Taken overall, these data do not support an increased risk of malignant neoplasms with liraglutide.

Malignant breast neoplasms were numerically imbalanced in the liraglutide weight management program, but evenly distributed in LEADER.

I will review in more detail both pancreatic and thyroid cancer since each is an identified area of interest for GLP-1 receptor agonists. The overall number of patients with pancreatic neoplasms confirmed by adjudication was 13 in the liraglutide arm and 5 for placebo patients.

When evaluating the pancreatic cancer events, it's important to take into account both the timing and the stage of the events. In the liraglutide group, the reporting rate did not increase over time, with 8 out of the 13 events identified within the first 18 months of the trial. This indicates no increased risk with longer

duration of treatment.

Furthermore, 7 of the 13 cases, confirmed cases for liraglutide, were classified as stage 4 at the time of diagnosis indicating that they were likely present at trial entry. This is consistent with the natural history of pancreatic cancer where many years are necessary before clinical symptoms arise.

As noted in the briefing documents, there were additional cases of investigator reported pancreatic neoplasms in the placebo arm, which were not confirmed by the EAC. These cases had features consistent with the clinical course of malignant pancreatic neoplasms but lacked tissue for histopathology, a key piece in the adjudication process for all neoplasms.

In addition to the LEADER trial, the clinical development programs in type 2 diabetes and weight management showed no increase of pancreatic cancer for liraglutide.

Similarly, in the postmarketing setting, based on more than 6 million exposure years for

Victoza, data have not suggested an association between liraglutide and pancreatic neoplasms. This includes a large prospective claims database study with over 32,000 type 2 diabetes patients who initiated liraglutide, and were propensity score matched to initiators of other diabetes therapies. This OPTUM study was a postmarketing requirement with the goal to specifically evaluate potential safety signals among patients using liraglutide.

During the five-year observation period that captured more than 50,000 patient-years of exposure to liraglutide, there was no increase in the risk for pancreatic cancer. From a non-clinical perspective, there was no evidence of an association to pancreatic cancer in studies of mice, rats, and non-human primates. Based on the totality of all the available data, an association between liraglutide treatment and pancreatic cancer is unlikely.

In 2014, the FDA and the EMA issued a joint statement in which they concluded that available information was insufficient to definitively link

GLP-1 receptor agonist exposure with pancreatic cancer. The LEADER results and other data, generated since 2014, do not change this conclusion.

Reviewing now the thyroid neoplasms, overall there was a similar incidence of malignant thyroid neoplasms between liraglutide and placebo in the trial. In regard to medullary thyroid carcinoma, LEADER provided the opportunity to follow a large population for a duration almost twice as long as the longest trial in the diabetes development program. No cases of MTC occurred in the liraglutide exposed population. In the placebo arm there was one case of MTC.

Medullary thyroid carcinoma is a rare cancer, and as part of our ongoing risk management, we will continue to systematically monitor for incident cases of MTC through an ongoing 15-year registry in the U.S. that includes all approved long-acting GLP-1 receptor agonists.

Looking now at hypoglycemia, in the LEADER trial the incidence of both confirmed hypoglycemia

and severe hypoglycemia was lower in the liraglutide group than in the placebo arm. This was seen even with the lower end of study A1c for liraglutide. 2.4 percent of patients receiving liraglutide and 3.3 percent of patients on placebo experienced a severe episode during the trial.

These results align with expectations, as GLP-1 receptor agonists are associated with a low risk of hypoglycemia unless they're combined with sulfonylureas or insulin.

As we heard earlier, patients in the placebo arm were more likely to need intensification of diabetes treatment in the trial usually with the addition on insulin. In accordance with this, most severe episodes occurred in patients who were concomitantly on an insulin therapy. Over 90 percent of the events occurred in patients on insulin, sulfonylureas, or both.

Looking more closely at severe hypoglycemia episodes, here we see the time course for severe hypoglycemia events. The difference between the two arms resulted in an estimated 31 percent

reduction in the risk of developing severe hypoglycemia over the duration of the trial, which is clinically meaningful particularly in this older population with CV risk.

To summarize, the five-year LEADER data reaffirmed that liraglutide safety can be managed by the existing safety labeling. Gallbladder disorders are currently addressed in the liraglutide label. In addition, we now have long-term data that show no increased risk for pancreatitis of neoplasms versus placebo.

In conclusion, the overall safety profile for liraglutide in this high-risk population aligned with the known safety profile based on the clinical development programs and seven years of postmarketing experience.

Thank you. I'll now turn the presentation to Dr. Buse to add his clinical perspective.

Applicant Presentation - John Buse

DR. BUSE: Thank you, Todd.

Good morning. I'm John Buse from the University of North Carolina. I've spent my life

engaged in research, clinical activities, and advocacy aimed at improving the care of patients with diabetes.

I've been very close to the LEADER trial, as I served as its signatory investigator. It has been an honor and a pleasure to serve in that role and to have the opportunity to speak with you today. As both a clinician and an investigator, I'd like to focus your attention on the clinical implications of the findings from LEADER.

Type 2 diabetes represents one of the most important chronic diseases in the United States. The prevalence of diabetes has nearly doubled in the last 20 years with 29 million Americans currently affected. This includes 15 percent of adults, 26 percent of those over the age of 65, and an estimated lifetime risk of about 30 percent, and these numbers are only increasing according to projections.

Hypoglycemia has emerged as a major clinical challenge in diabetes treatment. Emergency room visits and hospitalization rates for hypoglycemia

now exceed those for hyperglycemia, particularly in older individuals with type 2 diabetes requiring insulin.

While it is clear that good glucose control reduces the risk of microvascular complications, the roll of glycemic control in cardiovascular risk remains uncertain. There are few data to support that improved glucose control reduces the risk of cardiovascular events over 3 to 5 years.

Nevertheless, the LEADER trial shows cardiovascular benefits for liraglutide. This is important because cardiovascular events still occur at about two-fold excess in people with diabetes compared to those without, despite improved cardiovascular risk management in the United States.

Not only are cardiovascular events increased in patients with diabetes, but age-specific cardiovascular and all-cause mortality are increased two-fold. A number of studies published over the last five years have documented a 3 to 6 year loss in life expectancy associated with

diabetes.

Despite the large number of approved agents, there is a continued, large, unmet clinical need for agents that improve glucose control, have a low risk for hypoglycemia, and do not promote weight gain. These are the important traditional clinical endpoints for diabetes drugs.

Recently, there has been a regulatory focus on assuring that diabetes drugs are safe from a cardiovascular perspective, but from a clinical perspective, there is increasing focus on developing anti-hyperglycemic agents that will have a positive impact on cardiovascular outcomes. This need is particularly urgent in older, high-risk individuals who disproportionately represent the patients treated in clinical practice. It was on this background that liraglutide was developed and the LEADER trial was conducted.

As Dr. Marso explained, the current standard of care for diabetes specifically focuses on cardiovascular risk factor management. A structured approach to multiple cardiovascular risk

factors was recommended by the leadership of the trial and implemented by investigators and their staff according to this paradigm.

The results of LEADER are most remarkable because except form glycemic controls, these cardiovascular interventions were well implemented with high fidelity in both arms of the study. Even on top of comprehensive cardiovascular risk management, liraglutide reduced risk for cardiovascular events.

While the FDA guidance on cardiovascular outcomes trials has focused on establishing cardiovascular safety of diabetes drugs, I believe that a statistically significant benefit on the primary endpoint of an appropriately conducted trial with a 3-component MACE endpoint definition of cardiovascular death, non-fatal MI, and non-fatal stroke indicates a very important patient benefit. This has been a largely illusive outcome in diabetes care.

The robustness of the cardiovascular benefit would be supported when all three components have

individual hazard ratios below 1 and would be further supported by consistent findings for expanded MACE. Finally, an optimal trial outcome would further demonstrate a benefit on all-cause mortality. The LEADER trial demonstrated these outcomes with consistency across cardiovascular endpoints, confirming a clinically meaningful benefit.

You've seen these data previously, but let me explain what they mean to me and my work with patients with type 2 diabetes at high risk for cardiovascular events. The LEADER data allow us to change the conversation about diabetes care from one of lowering glucose in order to reduce the risk on microvascular complication over decades, to a conversation about reducing death, heart attacks, and strokes over 3 to 5 years. Now we can talk to patients about major life-changing endpoints that they care about within practical time frames.

Displayed here are calculations of the number needed to treat to prevent all-cause death across various medication approaches used for

cardiovascular risk reduction in patients with clinical cardiovascular disease. These treatments all have become the standard of care for patients with diabetes and were widely employed as concomitant medications in the LEADER trial.

Even on this background of effective standard of care therapies, each of which reduces the risk of death in a meaningful way, liraglutide provides substantial additional cardiovascular benefit. The reduction of risk seen with liraglutide is within the same range as the benefit seen with these other approaches.

The LEADER data add important new information to the long history of use and extensive exposure of liraglutide and provide reassurance in regard to previously identified safety concerns. Specifically, because of the double-blind nature of the trial and the blinded adjudication of endpoints, my patients and I can be confident in the adverse event results from the trial.

A lack of a signal with regards to

pancreatitis is particularly reassuring in light of supportive pharmacoepidemiology data. Combined with the reduced weight and hypoglycemia seen with liraglutide, LEADER provides for a compelling profile of safety and efficacy.

How do we translate these results into clinical application? My practice has a large number of individuals with complicated type 2 diabetes. They are older, have multiple comorbidities, and many have had or are at risk for potentially mortal or disabling cardiovascular events, despite aggressive attention to cardiovascular risk factors.

Liraglutide has already established its place as an effective glucose-lowering agent with a low risk of hypoglycemia whether used on a background of oral agents or insulin. Expanding the indication for liraglutide to include cardiovascular risk reduction in diabetes will increase the opportunities for patients to achieve better outcomes.

Thank you. I'll now return the presentation

to Dr. Moses to conclude.

Applicant Presentation – Alan Moses

DR. MOSES: Thank you John.

As outlined by Dr. Buse, liraglutide clearly provided cardiovascular protection as demonstrated in LEADER. These data further support the extensive body of efficacy and safety data collected since the U.S. approval of liraglutide in 2010 and its worldwide exposure in patients with type 2 diabetes. Ultimately, we need to consider the new findings from LEADER in the context of relative benefits and risk.

Overall, the results have reaffirmed the favorable benefit-risk balance of liraglutide for the treatment of type 2 diabetes. The 3-component MACE results from LEADER clearly demonstrate an atherosclerotic cardiovascular risk reduction, including a reduction in CV deaths, in individuals at high cardiovascular risk.

LEADER also demonstrated that liraglutide can reduce all-cause mortality. LEADER also reinforced the metabolic benefits of liraglutide.

These included A1c reduction with lower rates of hypoglycemia and lower use of insulin than the placebo standard of care group and clinically meaningful sustained weight loss. And for the first time, LEADER demonstrated that liraglutide is safe to use in elderly patients and in patients with chronic kidney disease and heart failure. No risks include gastrointestinal side effects that reduce tolerability and an increased risk of gallbladder events. Both of these currently are described in the Victoza label.

Data from LEADER also provide insight into areas of residual uncertainty. These include medullary thyroid carcinoma, pancreatitis, and pancreatic neoplasms. In each case, the totality of data based on LEADER, non-clinical data, completed clinical trials, as well as perspective claims database pharmacovigilance, do not support these potential risks, but also do not definitively rule them out.

The demonstrated benefits of the reduction in MACE and CV death clearly outweigh the potential

risks of liraglutide, which we will continue to follow through the ongoing MTC registry and routine pharmacovigilance.

Thank you for this opportunity to present the data from LEADER that support a new indication for liraglutide to reduce cardiovascular events in high-risk individuals with type 2 diabetes. We'll be happy to take your questions at this time. I'm going to change microphones very quickly.

Clarifying Questions to Applicant

DR. WILSON: Thank you very much.

At this point, we're open from the panel, the advisory committee, for clarifying questions that are going to be directed to Novo Nordisk. Please state your name as you are recognized and direct questions to specific speakers if you can.

DR. KONSTAM: Hi. Marv Konstam. Two questions. One, if you could put up slide CO-34 again, please? Just to clarify, and I think for the other p-values that you've shown, these p-values are one-sided p-values; is that correct? For the superiority value, the two-sided p-value

would be about 0.01; is that correct?

DR. MOSES: That's correct.

DR. KONSTAM: Okay. The other thing, if you could put up slide CO-42. I guess an issue for the panel is going to be -- even though as I understand there is no significant treatment by subgroup interaction, we're not seeing a favorable trend for the ITT analysis for North America. And so it poses the question, is there some difference?

Here you mention all the analyses that you've done. I think the panel would really benefit from more detail about these analyses. My own favorite is concomitant CV or diabetes medications. I'd be particularly interested in that, and other panelists may be particularly interested in other pieces of this.

DR. MOSES: Thank you Dr. Konstam. This slide shows the categories that we looked at. We have much more detail in terms of the variables shown on this slide. We've looked at all of these variables in the post hoc analysis, and none of these seem to explain the difference.

The only thing that we could identify in our evaluation, and it doesn't clarify whether this is a function of chance or whether it's a function of what I'm going to show you, is the fact that over time, the U.S. population, shown on this slide in the bottom two lines, whether on liraglutide in dark blue or placebo in light gray had a higher rate of permanent drug discontinuation, that is drug exposure, than those in the non-U.S. population.

This is part of the rationale or the underpinnings of the slide I showed during the core presentation, which demonstrated that the on-treatment analysis, taking into effect drug exposure, actually moved the hazard ratio to the left and resulted in our conclusion that this is probably the impact of actually individuals not taking the drug that is pushing the hazard ratio to the right.

DR. KONSTAM: Can you show us some details about the concomitant medications?

DR. MOSES: Yes. If we look at the forest

plot of both demographics, and at the bottom of the slide the concomitant medications -- now again, it's the categories of antidiabetes medications, antihypertensive, diuretics, and anti-thrombotic medications -- you can see overall that this does not change the overall hazard ratio for the North American population. This is not corrected for exposure. This is just for the total population.

DR. KONSTAM: I'm not quite clear how well this satisfies the issue. I'll just open this up, and I don't know how deeply you want to go into it right now. But obviously there's an array of other antidiabetic medications that are uptitrated, and they're uptitrated more in the placebo group than in the liraglutide group. One of the questions is could that be impacting the overall outcome, right?

Perhaps some of the other things that we're giving our patients may have adverse effects on cardiovascular health. For example, insulin is used more frequent, clearly more frequently, in the placebo group.

So I'd be curious about details of whether

there are specific antidiabetic agents, what is the practice -- is the practice in the United States different from practice outside of the United States? Are there specific antidiabetic medications that are uptitrated more frequently in the U.S. than they are outside of the U.S. that could be an explanation for the difference in cardiovascular events?

DR. MOSES: There are some differences between populations, as you might expect, even including drug availability in different regions of the world. But let's just look at one example, insulin versus non-insulin, if you will.

These are all post hoc analyses, of course, primary analysis at the top, and then in the bottom analysis, these are patients not on insulin. The hazard ratio is in the same range, and for patients on insulin, it did not push the hazard ratio to the right of 1. I could show you similar data for sulfonylureas and TZDs. Basically, the results are the same throughout.

DR. WILSON: Dr. Burman?

DR. BURMAN: Thank you. A couple of questions if I might --

DR. WILSON: Just as a reminder, Dr. Burman, state your full name so it goes on the record.

DR. BURMAN: Sure. Ken Burman. A couple of specific questions. The first is, Dr. Moses, you said there was consistent benefit across all CV components, but when I read the information it appears that non-fatal stroke, non-fatal MI, angina, revascularization, and hospitalization for congestive heart failure were not individually statistically significant, and the confidence interval was over 1. That's question number 1.

Question number 2 is, the baseline characteristics of the two populations were somewhat different with, for example, beta blockers, statin use, and platelet aggregation inhibitors being different in the two groups.

Number 3, I think I know the answer to this, but for thyroid cancer detection, you're just waiting for patients to have clinical disease, and I presume you're not doing anything more specific

or sensitive such as sonograms.

DR. MOSES: Let me answer the last question first if I might. That is correct. This was adverse event reporting by routine clinical surveillance, not active surveillance for thyroid disease, other than the calcitonin measurements that were measured throughout the course of the trial.

In regard to your first question, which was the individual components, you are correct that there was no statistical benefit for the endpoints other than cardiovascular mortality, and of course the primary endpoint, which was the most important.

This slide is from the core and shows the expanded MACE in each of the components you mentioned. But there was remarkable consistency in regard to the directionality of the hazard ratio, all to the left of 1, suggesting that the consistency of these findings is fully supportive of the expanded MACE result.

In regard to differences between the populations in the two groups, there were minor

differences only in terms of exposure. You're correct; there was a small difference in beta blockers. This did not account for the difference in the MACE events as assessed by the covariate analysis.

DR. WILSON: Dr. Blaha?

DR. BLAHA: Thank you. Mike Blaha. I want to go back a little bit to what Dr. Konstam was talking about with the U.S., with the North America population. I thought some of the data you presented was helpful, and I think it's somewhat convincing that there was a decrease in adherence I guess or use of the medicine in a sustained fashion in the U.S. or North America.

I would suppose that if the patients in the U.S. or North America were having decreased adherence or staying on the medicine less long, you might also see a diminution of the microvascular outcome or the HbA1c outcome, too.

Do you have microvascular outcomes or HbA1c outcomes dedicated for the North America group that we could look at?

DR. MOSES: Yes, and you're exactly right. In the North -- let's look at the hemoglobin A1c. I think this is most reflective of the acute effects of drug exposure. Shown here is the U.S. population to the left, the non-U.S. population to the right, same format that showed in the core for the overall population.

I think that you can appreciate that hemoglobin A1c decreased rapidly in both groups, but the slope of hemoglobin A1c in the liraglutide exposed population and the U.S. population actually was substantially steeper in an upward direction. We have other corroborating evidence to suggest that this is an exposure-related activity.

DR. BLAHA: Do you have microvascular outcomes, U.S.? Particularly kidney outcomes?

DR. MOSES: I'm not sure we have the U.S. population for the microvascular. If that's important to you, we can try to assess that during the break and return after lunch. Is that something you really wish to see?

DR. BLAHA: Love to see it.

DR. MOSES: Love to see it. Okay. So we'll try to get the microvascular -- the renal outcomes specifically in terms of microalbuminuria and the others.

DR. WILSON: Dr. de Lemos?

DR. DE LEMOS: James de Lemos. One major and one minor clarifying question. I'd like to see more detail on the confirmatory evidence that you had used to support this trial from the meta-analysis so that we can assess the robustness of those confirmatory data to support the single trial.

Then the minor point is I'd like to know a little bit more about what proportion of the MI events were silent and recognized on the EKG screening, and how sensitive the MACE endpoint was to the inclusion of silent myocardial infarction.

DR. MOSES: All right. Since the second is a somewhat easier question to answer, do you mind if I answer that first? Silent MIs were included in the primary endpoint throughout. They were assessed obviously by ECGs and readings at the CRO

by an experienced cardiologist before referral of changes to the adjudication committee. They represented about 20 percent of the total MIs.

Could I have, please, the forest plot? If you back silent MIs out of the primary analysis, there's no change. So directionally, there were fewer silent MIs in the liraglutide group than in the standard of care arm, and again when you, in a post hoc manner, remove those from the analysis.

If you're talking about the meta-analysis, you're referring back to the 3a development program? Is that correct?

DR. DE LEMOS: Correct.

DR. MOSES: Okay. Let's have the meta-analysis please from both the obesity, the weight management program, and the diabetes program. That's shown here. Now, there are slight differences between these. They're both characterized by relatively small numbers of events, and that's not surprising given the low risk of the population.

The meta-analysis in the weight management

program was actually a prespecified meta-analysis, and these events were adjudicated. In the type 2 diabetes program, they were post hoc adjudicated because there was no requirement for doing this analysis at the time of the original conduct of the trials.

Regardless, both show consistency in regard to the overall 3-component MACE and each of the individual components for both programs; again, the caveat being the relatively small number of events. But in totality when you put these two together, you're coming up with a MACE result completely consistent with that of the LEADER trial.

Does that answer your question?

DR. DE LEMOS: Yes.

DR. WILSON: Dr. Neaton?

DR. NEATON: Thanks. Jim Neaton. I have a question about the censoring for your MACE events for the time and event-driven analyses. Am I to understand this correctly that all of the patients were followed to a common calendar closing date?

DR. MOSES: That is correct.

DR. NEATON: And that date?

DR. MOSES: Excuse me. To a common calendar date? No. They were all followed to a minimum to 3 and a half years' exposure, and that was a function of --

DR. NEATON: I thought I read some place that you followed people, many people longer, because of the 18-month period of enrollment.

DR. MOSES: That's correct.

DR. NEATON: So were events counted for those people that were enrolled earlier after the 42 months?

DR. MOSES: Yes, absolutely. All events were counted during their duration of participation in the trial whether on drug or off.

DR. NEATON: How did you censor the end of follow-up? Can you explain it to me?

DR. MOSES: Kenneth Pil do you want to -- or Steve? Dr. Marso?

DR. MARSO: To answer your question, all events were accounted throughout the entire observation portion of the trial. It was a minimum

follow-up of 42 months, and because of the enrollment period, we did make the decision to do a staggered close-down of the clinical trial because patients had met the 42 months requirement, and we wanted to close down the trial in an efficient manner.

For the operational details, I will need to refer to Kenneth. But the overarching theme was we used a staggered close-down strategy, sites were closed down systematically, and all events were followed until the closedown of each site. But unlike some clinical trials where it ends on a specific calendar day, we did it in a staggered fashion.

DR. NEATON: So the calendar date varied by site.

DR. MARSO: Yes.

DR. NEATON: This may come up in the FDA presentation, but it relates to my questions. As I understood it from the briefing documents, there were some non-fatal events if they later died. Even if they died after the end of the study, they

were counted as deaths. Can you elaborate on that?

DR. MOSES: There were 3 individuals in total who had a cardiovascular death during the course of the trial who had had a prior first MACE before that cardiovascular death. Is that clear? So they were counted in the primary analysis for their first event --

DR. NEATON: For the first MI.

DR. MOSES: -- for the first event. If we include those in cardiovascular mortality, it does not change the outcome.

DR. NEATON: That's not exactly what I was asking.

DR. MOSES: I'm sorry?

DR. NEATON: If a person developed a non-fatal MI, and later the adjudication committee linked that non-fatal MI with the subsequent death, how was the patient classified, and what was their time to event?

DR. MOSES: Let me bring Anders Jespersen to the microphone to walk you through that specifically.

DR. JESPERSEN: Good morning. My name is Anders Jespersen, medical and science, Novo Nordisk, Denmark. Specifically for the linking between non-fatal MIs or myocardial infarctions to cardiovascular death, this was done by the chair of the adjudication committee who would review all subjects where there both was a confirmed cardiovascular death and a confirmed myocardial infarction, or a confirmed stroke.

He would then assess these, and if he evaluated that these were related -- and this he would do according to specifications in the adjudication charter -- then they would be linked. Then it would be the cardiovascular death counted in the time to first-MACE analysis.

DR. NEATON: The death was actually counted as the first event instead of the MI?

DR. JESPERSEN: Yes, if deemed related by the chair of the adjudication committee.

DR. NEATON: Was that true even for deaths that occurred after the closing date for a site?

DR. JESPERSEN: So the charter

specified -- or there was a guidance included in the charter specifying that the duration between the myocardial infarction and the death shouldn't exceed 30 days.

DR. WILSON: Is that satisfactory, Dr. Neaton?

DR. NEATON: I think I'll come back to it with the FDA presentation. I have to say that I'm not still very clear on the counting process here.

DR. WILSON: Low Wang?

DR. LOW WANG: Cecilia Low Wang. I have three points that I wanted to hear a bit more comment on. The first is on slide CO-44. I was wondering if you could comment on the very last line, which is the cardiovascular inclusion criteria.

The point estimate for patients who were enrolled under inclusion criteria number 3b had a point estimate that was 1.20, so I'd like to hear a little bit more about that.

Then two other points. One is could you comment on the difference between the risk for the

primary endpoint in patients with A1c above and below 8.3? And lastly, I'd like to hear from Dr. Hobbs in a little more detail on the EAC confirmed malignant pancreatic neoplasms.

DR. MOSES: Okay. Let's take them in order. For the so-called 3b inclusion criteria, as Dr. Marso indicated during his presentation, the inclusion criteria were defined not to establish cardiovascular disease but rather to establish criteria by which investigators could enroll patients at higher risk than was present in the phase 3 development program. And that was certainly achieved because the event rate in LEADER of 3.6 percent was doubled what we had anticipated or powered the trial for of 1.8 percent.

The challenge in this inclusion criteria 3b is it's a relatively small group, and we get into the issue of chance in terms of analyzing individuals who represented 10 percent of the events in the trial.

There was nothing distinctive about them to suggest that they were at much lower risk, other

than their overall event rate, which actually was 1.8 percent or exactly what we had predicted for the trial at the start of the trial.

We do not believe that this is a real finding based on the totality of the data and the primary prevention data that I showed you during the core.

Does that provide -- okay?

The second question, I'm sorry -- by baseline A1c?

DR. LOW WANG: Yes. So the difference in the -- depending on whether their A1c was above or below 8.3, actually, if your A1c was less than or equal to 8.3, the hazard ratio crossed 1.

DR. MOSES: Let's look at that in the core presentation because we didn't spend much time on it. That's shown here. It's the second bolded row, if you will, and is as you described. But let's look at it with a little more granularity, again recognizing the small subgroups here of the spectrum of A1c across the whole range that we saw on this trial.

Remember, you had to be above 7 to be in the trial, but some patients were above 7 at screening and below 7 at baseline, and they still made it in; that's very few. You can see that in all cases, the hazard ratio was to the left of 1. None of these group sizes are sufficient to achieve statistical significance, but the pattern, again, is completely consistent across the groups.

The third was Dr. Hobbs and pancreatic neoplasms.

DR. HOBBS: I'm not sure if there -- if I don't hit the specific area you would like to hear from -- but in general, in regard to the EAC confirm pancreatic neoplasms, the process, as you see, was designed to be very specific to identify those cases, tissue being a very important part of that diagnosis, again, ensuring high specificity, almost or actually all of the investigator reported cases were confirmed in the liraglutide arm. However, as I mentioned in the core, there were some cases in placebo that were not confirmed. And these 4 individual cases did not have tissue as

part of that process, so they were not able to have histopathology.

In addition, we had performed a sensitivity analysis of all investigator reported cases of potential pancreatic neoplasms. This is outlined a little more in both of the briefing documents, but overall, those numbers are fairly consistent between the 2.

To look at the cases that were mentioned in our presentation as well as in the briefing documents, these are the 4 cases in placebo that did not have the tissue available. Certainly, clinically they likely represent pancreatic neoplasms; in fact 3 of the 4 are likely adenocarcinoma of the pancreas and with features consistent with biomarkers and staging, et cetera, imaging, but again, without tissue.

I think if you're interested in more of the clinical picture, our expert Dr. Rustgi could speak to that, if that would be helpful?

DR. LOW WANG: What about the non-confirmed malignant neoplasms in the liraglutide group? You

showed the non-confirmed neoplasms in the placebo group. What about the other group, the liraglutide group?

DR. HOBBS: They were all confirmed.

DR. MOSES: All were confirmed in the liraglutide. There were a total of 13 cases referred into the adjudication committee. All were confirmed.

DR. LOW WANG: Okay. Thank you.

DR. WILSON: Next question from Mr. Oakes by phone. Dr. Oakes?

DR. OAKES: I actually have a comment briefly on the on-treatment analysis looking at the U.S. patients, but I think it will be more appropriate to compare on-treatment in the U.S. with on-treatment in the rest of the world, rather than with the entire analysis for the rest of the world. I don't expect the results to be very different.

My other question relates to the basis of the sample size calculation. As I understand it, there was no sample size calculation done for

efficacy. The sample size was based on the non-inferiority test.

Is this correct?

DR. MOSES: That is correct.

DR. OAKES: A sort of corollary to that is that there was never any kind of specification of what a clinically meaningful effect size would be to demonstrate efficacy.

DR. MOSES: In terms of cardiovascular outcomes, I'm going to actually ask Dr. Marso to come to the microphone to describe that because I believe that a statistically significant reduction, of course within reasonable sized trials, would provide clinical meaningfulness.

DR. MARSO: I have one comment about the power and sample size estimates, and that is true that we powered it for the non-inferiority assessment. But given the 42-month minimum duration, we actually accrued a substantial -- greater number of events than we had powered the trial for. So that would be my first comment, an unintended consequence of the risk of

the population and the duration of follow-up.

I guess my comment about clinically meaningful, I guess it's in the interpretation of the data, isn't it? It's a statistically significant finding, and at least in my interpretation, given the unmet need for diabetes and cardiovascular disease, the background risk of CVDs, a relative risk reduction that we saw both here with a primary endpoint and for CV death is clinically meaningful and I think needed in the field frankly.

DR. OAKES: I'm certainly not disagreeing with that, but I do find that it's unusual in a demonstration of efficacy not to see some statement of what the power is to detect a specific level of efficacy.

I guess a sort of related comment, which has been made, is that the actual event rate was very much greater than that was specified. I'm curious as to what extent that was because of a sort of --

DR. MOSES: I'm sorry, Dr. --

DR. OAKES: -- intent to include patients

at higher risk in the study.

DR. MOSES: The original intent wasn't an intent, but the thought was that 70 percent of the patients likely would come from the lower risk category not the higher risk. This was the first cardiovascular outcome trial that we had conducted enrolling in a diabetes population.

The event rate of 1.8 percent was consistent with that from the literature and a variety of other event rates for cardiovascular outcome trials. Of course it varies dramatically on the population, and also on the year with improved treatment.

The higher event rate was in fact a result of having a greater percentage in the higher risk population, and that was just a benefit from accrual and enrichment. So the enrichment process worked, as Dr. Marso had said.

DR. OAKES: Okay. Thank you.

DR. WILSON: Dr. Budnitz?

CAPT BUDNITZ: Thank you. Dan Budnitz. This is a question for Dr. Moses about the

bothersome U.S. subgroup finding and adherence rates. And I'm wondering, this low adherence rate in the U.S., is that similar to other studies with liraglutide, or is this a unique finding to LEADER? Does the sponsor have an explanation for this lower adherence rate in the U.S.?

DR. MOSES: It is not unique to LEADER or liraglutide. I don't want to impugn the U.S. population and healthcare system, but we have conducted three cardiovascular outcome trials over the last number of years, LEADER to your left here, another trial that's actually been reported in the literature but not yet reviewed by the FDA, and another trial that has just been submitted to the FDA and was reported at the ADA.

Here you see in orange the U.S. population, and then you see the non-U.S. population in terms of treatment discontinuation. It is an unfortunate consistent finding, at least in our hands, and I believe in many other investigators hands as well.

CAPT BUDNITZ: And just to follow, any explanation or interventions in --

DR. MOSES: It would be inappropriate for me to -- based on the data we have, to try to hypothesize the reasons behind it.

DR. WILSON: Dr. Robbins?

DR. ROBBINS: I may have missed this, but were all of the patients treated with 1.8 milligrams per day? If not, what percent were on lower dose? And if so, is that percentage similar to what's being used in the clinical population in the U.S.?

DR. MOSES: It's a more difficult question to answer than you might expect. What we have is exposure to the different doses. The request, the protocol was that patients were to be escalated to the 1.8 milligrams if they could tolerate it. If they could not because of GI side effects, some actually remained on a lower dose. What we don't have -- we have the exposure by dose. We don't have the exact number of patients by dose because there was some movement between different doses over the course of the trial.

To the question about is this similar to

what we see in clinical practice, in the United States, the majority of patients actually are on 1.8 milligrams, not quite this high a percentage as we saw in LEADER, however.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: Thank you. Yves Rosenberg. Still a follow-up on this issue of a difference between U.S. and other countries. First, you must have some information about the causes of drug discontinuation, I assume, as is reported. So it would be interesting to have some descriptive data.

Second, still on the same issue, I don't think you really answered Dr. Konstam's issue at the beginning about descriptive analysis of the use of drugs in this population and the differences. The data you presented showing the difference between insulin versus no insulin and the statement you made, I'm not sure answers that question.

I'm very puzzled by the statisticians' comment, all this fuss about the subgroups that provides such difference because they are not adjusted for the other differences. People who may

take insulin may have many other different characteristics in term of age of risk, so I think these are very dubious if they are not further and better analyzed. That's the first other question.

Second, can you comment on the potential of missed events? You described that there were many ways that events were reported, but how was the monitoring done? Were many visits that were missed and not reported, detected through this use, that maybe guess there's a bigger problem there? And hopefully, it will show that there isn't.

Third, the question is related to unstable angina. In the EAC table, there's an unbalance in the favor of liraglutide, but in the analysis of the expanded MACE there's no difference. I assume it's because of the definition and the education, so I'd like you to expand on the definition on unstable angina use here. Thank you.

DR. MOSES: Okay. So a number of questions. Let me start with the first of those, which was the reasons for permanent drug discontinuation in the U.S. population. We did investigate that. One of

the challenges is the fact that the most frequent categories for discontinuation were other or no reason, so not very insightful. I will point out again this was not unique to liraglutide. It actually occurred even more for placebo for all of these different categories.

Is that sufficient in terms of lack of explanation I'm afraid?

DR. ROSENBERG: U.S. versus non-U.S.

DR. MOSES: We can show you U.S. versus non-U.S. Sorry for the complexity of the table. There are a lot of rows and columns here.

You'll first note that the number of patients in the non-U.S. is higher, so the absolute numbers you're going to see there, but look instead at the percentage. You can see that the permanently discontinued was clearly higher in the U.S. population for both liraglutide and placebo versus non-U.S.

Again, the category most often seen is that of other or no reason for drug discontinuation. There were no major differences in terms of the

pattern of drug discontinuation, although it was lower in the non-U.S. population.

Should we go on to -- I'm not sure exactly how you want to see the data for drug exposure. Why don't we show the baseline and then post-baseline U.S. population and non-U.S. population, so the bar graphs that we have.

We did look at this. Now it may not have the granularity you're seeking because it's still in categories, but I think it is nonetheless instructive. Here is the baseline profile, and this gets to one of the other questions asked about beta blockers earlier, although not that specifically.

It's the concomitant medications at baseline in the U.S. and non-U.S, U.S. in orange and non-U.S. in blue. And you can see that they're roughly comparable, there's a little bit more lipid-lowering agents in the U.S. and platelet aggregating inhibitors in the U.S. But as far as antihypertensives, very close, perhaps a little bit more of diuretics.

DR. KONSTAM: Can I just ask, you saying concomitant medicines. What about medications started post-randomization?

DR. MOSES: That's what I'm going to show you next.

DR. KONSTAM: Okay. And you're going to show for antidiabetic drugs as well, I assume?

DR. MOSES: I can do that, yes. This is first for the CV medications, but we also have it for the diabetes medications.

This slide, again U.S. at the top and non-U.S. at the bottom, liraglutide in blue here placebo in gray, and you can see the addition of these medications, again, by class. Remember, there's a high baseline to start with, but this is the pattern of addition of medications.

What it shows is that, in fact, there were more medications added in both the U.S. and the non-U.S. in the non-liraglutide treating arm. So if these are effective as cardiovascular protection, they would, if anything, reduce the difference between the two groups.

Is that satisfactory for antihypertensives, and I'll move on to diabetes medications?

(Dr. Rosenberg nods in the affirmative.)

DR. MOSES: Yes? At baseline -- now this is again, Dr. Konstam, at baseline, and I'll show you in a moment the post-baseline. But these are the antidiabetes medications. A little bit more insulin use in the U.S. and a little bit more non-insulin use in the rest of the world at baseline.

Now if we look post-baseline, again you can see that regardless of whether it was in the U.S. or non-U.S., the group that were not on liraglutide, on the placebo standard of care arm, added more medications, as you would expect, to try to bring their hemoglobin A1c down.

DR. WILSON: I think we're going to take a break right now. We have some other committee members who have questions, and we'll come back to that later this morning.

What time shall we come back? Ten minutes? 10:20, right? 10:20. I have 10:08, so 12 minutes.

(Whereupon, at 10:08 a.m., a recess was taken.)

DR. WILSON: All right. I think we're getting organized for our next section. For the advisory committee members who had -- we have your names for questions. We're going to plan to get back to those after the FDA presentation. Our next is FDA presentations.

FDA Presentation - Tania Condarco

DR. CONDARCO: Good morning. My name is Tania Condarco, and I'm a clinical reviewer in the Division of Metabolism and Endocrinology Products. On behalf of the review team, I would like to thank the committee for being here today.

Today, we will present the FDA's review of the liraglutide effect and action in diabetes, evaluation of cardiovascular outcome results, which will be referred to as the LEADER study throughout the presentation.

After this brief introduction, I will provide an overview of the liraglutide-containing products that are approved and discuss the

regulatory history preceding the conduct of LEADER. I will follow this with a description of the LEADER trial design, objectives, patient disposition, and baseline characteristics.

Dr. Kiya Hamilton will then present the FDA statistical assessment. After this, I will return to discuss the clinical interpretation of CV death, cardiovascular safety, and microvascular endpoints. Dr. Julie Golden and Dr. Shannon Sullivan will then discuss non-cardiovascular safety findings.

Liraglutide is a glucagon-like peptide-1 analog with prolonged GLP-1 receptor agonist activity. Liraglutide is approved for the treatment of type 2 diabetes as an adjunct to diet and exercise to improve glycemic control as a single agent under the trade name Victoza, and in combination with insulin, degludec under the trade name Xultophy 100/3.6.

Liraglutide under the trade name Saxenda is also indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in obese and overweight patients

with weight-related comorbidities.

At the time of Victoza's approval, a postmarketing requirement, or PMR, was issued to address postmarketing cardiovascular safety and safety issues of interest. LEADER was primarily designed to address the postmarketing cardiovascular risk of liraglutide, and thus intended to rule out a 30 percent excess CV risk and to address additional safety issues of interest noted at the time of approval. These included calcitonin, a medullary thyroid cancer biomarker, as will be discussed later, pancreatitis, renal safety, serious hypoglycemia, immunological reactions, and neoplasms.

LEADER was a time and event-driven randomized, double-blind, placebo-controlled trial in adults with type 2 diabetes and established cardiovascular disease in patients with cardiovascular risk factors. The trial duration was dependent on all patients having a minimum treatment period of 42 months and a total of at least 611 confirmed MACE events.

After the 2 to 3 week run-in period, patients were randomized 1 to 1 to either liraglutide or placebo. Liraglutide or placebo was added to local standard of care drugs for both diabetes and atherosclerotic cardiovascular disease. Patients were treated for traditional cardiovascular risk factors and glucose goals according to local standard of care.

The primary endpoint was time to a first major adverse cardiovascular event, or MACE, consisting of the 3-part composite of the cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

Secondary endpoints included time to the composite expanded MACE, which was made up of the three components of MACE with the addition of coronary revascularization, hospitalization for unstable angina pectoris, and hospitalization for heart failure. Additional secondary endpoints included time to the individual components of expanded MACE and time to all-cause death.

LEADER had an independent blinded event

adjudication committee. The committee was responsible for central adjudication of all-cause deaths, MACE, expanded MACE, and selected events of interest, based on standard definitions as shown in Appendix 1 of the briefing packet.

The four subcommittees of the EAC are shown here. The cardiovascular subcommittee adjudicated deaths from any cause, while the neoplasm, pancreatitis, and microvascular subcommittees adjudicated each of these safety events, respectively.

The study population was enriched with type 2 diabetic patients at relatively high risk for MACE events to facilitate event accrual. Either of two criteria needed to be met. The first criterion included patients with an age of at least 50 years with type 2 diabetes and a history of myocardial infarction; cerebrovascular disease; peripheral vascular disease; New York Heart class 2 to 3 heart failure; arterial stenosis above 50 percent for coronary, carotid, or lower extremity arteries; evidence of symptomatic or asymptomatic ischemia;

or an estimated GFR of less than 60 mLs per minute; in other words, patients with moderate and severe chronic kidney disease.

The second criterion included patients with an age of at least 60 years with microalbuminuria or proteinuria, or who have cardiovascular risk factors such as hypertension and left ventricular hypertrophy, or left ventricular dysfunction, or an ankle brachial index less than 0.9.

A total of 12,076 patients were screened, and 2,736 patients withdrew before randomization by being either screen failures, most of whom did not meet the hemoglobin A1c inclusion criteria of 7 percent of above, or withdrew due to lack of meeting the randomization criteria, which included adherence to at least 50 percent of the injection regimen or by having a calcitonin level above 50 nanograms per deciliter.

In total, 9,340 patients were randomized 1 to 1 to liraglutide or placebo. The observation time or time on study was approximately 3.8 years, while the exposure time or time on treatment was

approximately 3.5 years for either treatment.

Of all patients randomized, 99.8 percent were exposed to trial product. About 97 percent of patients randomized to liraglutide or placebo completed the trial. Completer patients were defined as having a MACE event, non-CV death, or having direct contact with the investigator at the follow-up visit.

Of the roughly 3 percent of patients that did not complete the trial, reasons for withdrawal included loss to follow-up or withdrawal of consent. For the majority of these patients, however, vital status was available. In fact, over 99 percent of patients were either completers and/or had known vital status in both treatment groups.

This table displays the demographics and baseline characteristics for all patients randomized into the trial. The patient characteristics were generally similar across arms. In both arms, patients had a mean age of 64 years. Women made up more than a third of patients. More

than three-quarters of the patients were categorized as white race.

The average duration of diabetes was over 12 years. The average estimated GFR was 80. Approximately 4 percent of patients in either treatment were treated with only diet and exercise, while over a third were using insulin in combination with oral antidiabetic therapies.

The baseline incidence of diabetic complications was also balanced between treatment groups with nephropathy present in approximately 40 percent of patients. Over 90 percent of patients had hypertension, and more than half of patients were previous or current smokers.

This figure shows the baseline characteristics of the randomized patients by cardiovascular inclusion criteria. Approximately 80 percent of patients had established cardiovascular disease or chronic kidney disease and were 50 years of age or more, as shown in the shaded green area. The most common risk factors within this group were peripheral vascular disease

and history of MI.

I will now turn the presentation over to our biostatistician, Dr. Kiya Hamilton, to review the statistical efficacy overview.

FDA Presentation - Kiya Hamilton

DR. HAMILTON: Good morning. My name is Kiya Hamilton. I am the primary statistical reviewer of the application being discussed today. I will present a quick overview of LEADER, followed by the key trial results and a summary of the findings. I will now begin with a brief overview of the LEADER trial.

The primary objective of LEADER was to demonstrate safety with non-inferiority of liraglutide against placebo for major adverse cardiovascular events or MACE. The trial was designed to rule out a 30 percent or greater increase in cardiovascular risk when compared to placebo.

The primary endpoint was time from randomization to first occurrence of MACE, which included cardiovascular death, non-fatal MI, and

non-fatal stroke. A Cox proportional hazards model was used for the primary analysis. The model included study treatment as a factor. Hazard ratios for liraglutide versus placebo were estimated from Cox model results.

In order to be considered non-inferior to placebo, the upper limit of the 95 percent confidence interval for the hazard ratio needs to be below 1.3; in other words, to rule out a 30 percent increase in MACE for liraglutide compared to placebo. If a 30 percent increase and the risked cardiovascular events is ruled out for MACE, then a test for superiority of liraglutide versus placebo will be conducted. When concluding superiority against placebo, the upper limit of the 95 percent confidence interval for the hazard ratio needs to be below 1.

Along with the primary endpoint of MACE, I will also discuss time to first occurrence of cardiovascular death, which is a component of the MACE endpoint. Additionally, I will present the results of total MACE, which is made up of total

MI, which is made up of fatal MI and non-fatal MI; total stroke, which is made up of fatal stroke and non-fatal stroke; and all-cause death.

These time-to-event endpoints were analyzed using the Cox proportional hazards model with a study treatment as a factor. The proportion of events and the hazard ratios will be presented.

Here are the key trial results. All analysis presented here were performed using the full analysis set, which was defined as all randomized patients. A Kaplan-Meier curve of the MACE endpoint is shown here. The X-axis represents the time from randomization in months, from month 0 to month 60. The Y-axis represents the probability of being MACE-free.

Below the figure is the number of patients still being followed for an event. The red line represents liraglutide probability, and the blue line represents placebo probability. We see a clear separation between the 2 curves of liraglutide and placebo throughout follow-up.

The total number of patients experiencing

MACE during the study period was 608 or 13 percent for liraglutide and 694 or 15 percent for placebo. The hazard ratio from randomization to first occurrence of MACE was 0.87, with an upper bound of 0.97.

This corresponds to a relative risk reduction of MACE of 13 percent for liraglutide versus placebo. We see the hypothesis for ruling out a 30 percent increase in the risk for cardiovascular events is met since the upper bound for MACE is below 1.3.

Additionally, the upper bound for MACE was below 1, which meets the criterion for showing superiority for this endpoint. This means this result supports cardiovascular benefit when comparing liraglutide to placebo.

Of the 608 patients who experienced MACE in the liraglutide group, 181 had a cardiovascular death, 275 had a non-fatal MI, and 152 had a non-fatal stroke. Correspondingly, in the placebo group, 227, 304, and 163 patients had those same events.

Now I will cover the results for the MACE-related endpoints, cardiovascular death, which is a component of MACE; as well as total MI, total stroke, and all-cause death.

The following bar charts provide the proportion of patients with events for the treatment groups. Liraglutide is represented in red, placebo is represented in blue.

This table shows a proportion of patients that experienced a cardiovascular or CV death. Of the components of MACE, this component of CV death had the largest difference between treatment groups in the number of patients experiencing an event. 219 or 4.7 percent of patients had a CV death in the liraglutide group compared to 278 or 6 percent in the placebo group. The hazard ratio of 0.78 corresponds to a 22 percent risk reduction of a CV death occurring in the liraglutide group compared to placebo.

Here we see the proportion of patients who experienced an MI during the trial. Total MI is the sum of fatal MI and non-fatal MI. There were

more events of MI than there were of CV deaths. 292 or 6.3 percent of patients in the liraglutide group compared to 339 or 7.3 percent in the placebo group had an MI. The hazard ratio of 0.85 corresponds to a 15 percent relative risk reduction of a total MI occurring in the liraglutide group compared to placebo.

The proportion of patients who experienced a stroke are presented on this slide. Total stroke is made up of fatal stroke and non-fatal stroke. Total stroke had the smallest number of events, 173 or 3.7 percent of patients in the liraglutide group compared to 199 or 4.3 percent in the placebo group. The hazard ratio of 0.87 reflects a 13 percent relative risk reduction of total stroke occurring in the liraglutide group compared to placebo.

The bar chart presented here provides a proportion of patients who experienced all-cause death. All-cause death is a total of CV death and non-CV death. The shaded region represents a proportion of patients experiencing a CV death for

liraglutide and placebo. The solid region represents a proportion of patients experiencing a non-CV death for liraglutide and placebo.

The percent above each bar shows the total all-cause death for each treatment group. The difference in all-cause death was driven by the difference in CV death, as a greater portion of patients experience a CV death compared to a non-CV death.

As mentioned earlier, 4.7 percent and 6 percent of patients in the liraglutide and placebo groups, respectively, had a CV death. 162 or 3.5 percent of liraglutide patients and 169 or 3.6 percent of placebo patients experienced a non-CV death. In total, 381 or 8.2 percent of patients experienced an all-cause death in the liraglutide group compared to 447 or 9.6 percent in the placebo group.

Here we see the hazard ratios of MACE, all-cause death, total MI, and total stroke presented together. We used the same Cox proportional hazards model from the primary

analysis to estimate hazard ratios and 95 percent confidence intervals for these MACE-related endpoints.

There is a line drawn at 1 to illustrate where the hazard rates would be considered the same between the two treatment arms. The hazard ratios of the related endpoints fall in line with the hazard ratio of MACE, which supports the primary endpoint. However, the hazard ratios for total MI and total stroke have upper bounds that are at or greater than 1.

I will now show the results of the subgroup analysis for MACE. This plot presents the subgroup analysis for MACE. The subgroups age is 65 or older versus below 65; sex; region, outside of the U.S.A. versus USA; and race, Asian, black, other, and white are either required by federal regulations or recommended by FDA guidance. The hazard ratio for the U.S.A. is 1.03, which is in the opposite direction as primary MACE. Dr. Condarco will further discuss this result.

This LEADER trial was successful in ruling

out at least a 30 percent or greater increase in cardiovascular risk for the primary endpoint in MACE. In addition, superiority of liraglutide against placebo was shown for MACE and CV death. Superiority was shown in all-cause death of liraglutide over placebo. This was due to the large difference in the CV deaths.

This now concludes my portion of the presentation. I will hand it back to Dr. Condarco. Thank you.

FDA Presentation - Tania Condarco

DR. CONDARCO: I will now discuss the findings of cardiovascular safety, CV death, non-CV death, and the results of the microvascular efficacy endpoints. I will begin by discussing the subgroup analyses of MACE.

The sponsor performed multiple prespecified subgroup analyses of MACE, as shown in figure 7 in the Novo Nordisk briefing document. Among these analyses, point estimates of the hazard ratios above 1 were observed. This could suggest possible inconsistency in the effect for MACE across these

subgroups. The two subgroups I will talk about are regional subgroups, and the cardiovascular history subgroup. Because of these findings, additional exploratory analyses were performed. I will first discuss the analyses of the regional subgroup.

This is FDA's analysis comparing the effect size in the U.S. subgroup versus the non-U.S. subgroup. The hazard ratio for MACE in the U.S. subgroup was 1.03 with an upper bound of the 95th confidence interval of 1.25. Twenty-seven percent of randomized patients were from the U.S. The p-value for interaction was 0.048. This is marginal evidence that the size of treatment effect may be different between these subgroups. However, there is no strong evidence that the direction of treatment effect was different.

This interaction is worth noting because approval of a cardiovascular benefit indication would be based on the assumption that the overall trial results are applicable to the U.S. patients and the U.S. standard of care.

The sponsor explored differences in baseline

characteristics between the U.S. and non-U.S. population. As shown in this table, the U.S. population had a higher BMI, lower systolic/diastolic blood pressure and total cholesterol, longer diabetes duration, slightly higher hemoglobin A1c, and lower mean eGFR. However, as the sponsor noted in the briefing document, none of these individual differences were able to account for the observed difference in treatment effect on MACE between the U.S. and non-U.S. subgroups.

Evaluation of baseline medications also revealed slight differences between the U.S. and non-U.S. subgroups. At baseline, patients in the U.S. used more insulin, more diuretics, more lipid-lowering drugs, and more platelet aggregation inhibitors.

The sponsor again, concluded that none of these individual differences accounted for the treatment effect differences on MACE between the U.S. and non-U.S. subgroups. It is unknown how the multiple differences in aggregate could have

influenced a U.S. subgroup findings for MACE.

Another difference that was noted between the U.S. and non-U.S. subgroups was time on trial product. In the previous slides, I showed baseline differences between the U.S. and non-U.S. subgroups. Here, I would like to emphasize that this is a post-randomization difference.

Novo Nordisk performed several on-treatment sensitivity analyses presented in their background document, and based on the results of these analyses concluded that lower exposure in the U.S. population may have explained the U.S. subgroup findings.

It is not clear to us that the applicant's selected analytical methods were the most appropriate way to address the question. We are therefore not prepared at this time to endorse the concept that exposure can explain the U.S. findings if real.

Additionally, the sponsor conducted an analyses including the evaluation of the rate of first MACE in the placebo group for the U.S. and

non-U.S. subgroups. These analyses showed that the rate of MACE events in the U.S. was not lower than expected and was similar, in fact, to the rate of MACE in the non-U.S. population. In addition, there were no notable differences in the treatment response for hemoglobin A1c, body weight, and systolic blood pressure between the U.S. and non-U.S. group.

The other subgroups showing a point estimate of the hazard ratio above 1, was the subgroup of patients 60 years of age or older with cardiovascular risk factors. Nineteen percent of the randomized patients were in this subgroup, but this subgroup accounted for only about 10 percent of first MACE events.

The p-value for interaction was 0.04. This is marginal evidence that the size of treatment effect may be different between these subgroups. However, there is not strong evidence that the direction of the treatment effect was different. This interaction is worth noting from a clinical standpoint because the applicant seeks an

indication for both primary prevention and secondary cardiovascular disease prevention.

In summary, point estimates of the hazard ratios were above 1 for the U.S. subgroup and for patients with age greater than 60 with risk factors. This could suggest possible inconsistency in the effect of MACE across these subgroups. Several analyses were conducted to explain these findings, but it is important to emphasize that these were exploratory, and there still remains a possibility that the subgroup findings could be explained by chance alone.

I will now turn to discuss the components of MACE. For both liraglutide and placebo, the largest component of the MACE endpoint was made up by non-fatal MI. There were a total of 275 non-fatal MIs for liraglutide and 304 for placebo. As you can see, most of the events were non-ST elevation MIs rather than ST elevation MIs. With regards to symptomatic versus silent MIs, most were symptomatic, and when evaluated by types of MIs, the majority were classified as spontaneous MIs.

This table shows the types of non-fatal strokes, which contributed to the MACE endpoint. There were a total of 152 non-fatal strokes for liraglutide and 163 for placebo. Ischemic strokes were seen in over 85 percent of patients who had a stroke with a smaller percentage of hemorrhagic and undetermined strokes.

I will now discuss the mortality findings in LEADER. As discussed by Dr. Hamilton, all-cause mortality was lower for liraglutide than placebo with the results being primarily driven by CV death. I will now discuss the causes of death in more detail.

The category of CV deaths were composed of both known causes of CV deaths and unknown causes of CV deaths, as shown bolded in the table. Most cardiovascular deaths had a known cause of which sudden cardiac death was the largest subcategory, followed by fatal MI, cardiogenic shock, and fatal stroke. The category unclassifiable included events where 2 adjudicators did not enter a comparable cause of death for a specific event,

while the category death due to other CV cause included vascular events, such as a ruptured aortic aneurysm or thromboembolic disease.

Close to 30 percent of the cardiovascular deaths in either treatment arm were due to an unknown cause as defined in the EAC charter deaths for which there was no clearly documented thrombovascular cause.

Of the deaths with unknown cause that were adjudicated as CV deaths, death certificates were available for approximately a third, with less information available from autopsies or death registries.

This slide shows two sample narratives for unknown causes of death. In the first example, a 59-year-old male with history of hyperlipidemia, myocardial infarction, heart failure, ischemic heart disease, left ventricular systolic dysfunction, and hypertension suddenly collapsed after walking for 30 minutes. There was no documentation of the death.

In the second example, a 67-year-old male

with history of an abdominal aortic aneurysm, hypertensive heart disease, stable angina pectoris, and hypertension, was reported as having a witnessed death. The cause of death was reported as unknown on the death certificate.

As these examples demonstrate, there was little information available for most of these unknown causes of death. Nevertheless, categorizing unknown causes of death as CV death is an accepted approach for these cardiovascular outcomes trials. Based on these narratives, it is not unreasonable to attribute these deaths to a cardiovascular cause.

This table shows the non-cardiovascular deaths as classified by the sponsor. The most common reported cause of death were malignancies and infection. Based on these subcategories, the causes of death were similar between treatment groups with slight differences in the number of adjudicated renal deaths not in favor of liraglutide. Renal safety will be discussed shortly by Dr. Golden.

I will now discuss additional cardiovascular safety topics including parameters that may influence CV risk. This figure shows the mean heart rate by visit in the trial. Both liraglutide and placebo had a similar baseline. However, after 6 months, the mean heart rate increased and remained elevated for liraglutide as compared to the placebo.

After three years, the change in the mean heart rate was higher by approximately 3 beats per minute in the liraglutide group compared to the placebo group. These findings are consistent with what is already labeled for liraglutide.

This figure shows the mean systolic blood pressure over time for liraglutide and placebo. At baseline, systolic blood pressure was similar between treatment groups. As a reminder, at baseline, over 90 percent of patients had a history of hypertension and were on antihypertensive therapy. After baseline, the liraglutide group experienced a mean decrease in systolic blood pressure, noted at month 6.

Despite some variation of blood pressure during the trial, the systolic blood pressure remained lower for liraglutide than placebo at any point in the trial, and was numerically lower by 1.3 millimeters and mercury for liraglutide versus placebo at the end of the trial.

This figure shows the mean diastolic blood pressure over time for liraglutide and placebo. For both treatment groups, there was an overall decline in diastolic blood pressure over the course of the trial. However, this decline was less for liraglutide than with placebo with a difference of about half a millimeter of mercury higher for liraglutide than placebo at the end of trial.

Overall, there were 3 percent more patients who began antihypertensive therapies in the placebo group than in the liraglutide group after baseline. As shown in this table, this difference applied across antihypertensive drug classes.

This figure shows the mean hemoglobin A1c over time for liraglutide and placebo. Both groups started with a similar baseline hemoglobin A1c.

After 3 months of treatment, the liraglutide group showed a marked reduction in hemoglobin A1c, in contrast to the placebo group. Although the protocol specified that both groups be treated with standard of care antidiabetic therapies, the reduction in A1c was slightly greater in the liraglutide group at the end of the trial.

When considering antidiabetic medications started exclusively after baseline, more patients in the placebo group started antidiabetic therapies, including insulin, relative to the liraglutide group.

The specific medications initiated post baseline are shown in this table. Post baseline, 7 percent more patients began taking non-insulin antidiabetic medications and 14 percent more patients began insulin in the placebo group, relative to the liraglutide group.

The particular increase in treatments with sulfonylureas, glinides, and insulin treatment for placebo may help elucidate the severe hypoglycemia findings in LEADER.

The percentage of patients experiencing a severe hypoglycemia event was slightly lower in the liraglutide group, although at baseline, 90 percent of patients with severe hypoglycemia were using sulfonylureas, glinides, or insulin. The post baseline relative increase of the use of these medications in the placebo group, as compared to the liraglutide group, could have resulted in the observed severe hypoglycemia rates in LEADER.

This figure shows the mean body weight trends over time for liraglutide and placebo. Although both groups started with a similar baseline body weight, over time, there was a larger decrease in weight for liraglutide than placebo with a numerical difference of about 2 kilograms lower for liraglutide than placebo at the end of trial.

There was no differences in lipid parameters between treatment groups. This slide shows the trends for lipid measures over time for total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Slightly more patients in the

placebo group started lipid-lowering therapies after baseline, as shown in this table.

While there were differences in heart rate, blood pressure, glycemic control, and body weight seen in LEADER, it is unclear how these contributed to the overall assessment of MACE.

I will now discuss the microvascular efficacy endpoints and the issues that affect the interpretability of these results. The microvascular endpoints were prespecified and included a composite of retinopathy and nephropathy components. These endpoints were identified based on either investigator reported adverse events, laboratory findings, or both. An adjudication of these endpoints was conducted by the microvascular subcommittee of the EAC.

The retinopathy component included the need for retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, or development of diabetes-related blindness. The renal component included new onset of persistent macroalbuminuria, persistent doubling of creatinine

with an eGFR of less than or equal to 45, initiation of continuous renal replacement therapy, and death due to renal disease.

As shown in this table, a smaller proportion of patients in the liraglutide group met the composite microvascular disease endpoint compared to the placebo group. However, this endpoint was largely driven by the nephropathy composite and more specifically macroalbuminuria.

In addition, the retinopathy and nephropathy components of the microvascular endpoint had opposite trends. While the first EAC confirmed nephropathy events favored liraglutide, the retinopathy findings generally favored placebo.

I will now discuss the retinopathy and nephropathy composites in detail beginning with the retinopathy endpoint analyses.

At baseline, over 70 percent of patients in either treatment arm had no retinopathy. The presence or absence of diabetic retinopathy was unknown in 8 percent of patients, and approximately 20 percent of patients had either

non-proliferative, proliferative, or retinopathy that was not specified.

Investigators were not required to perform routine clinical ophthalmological assessments at any point during the trial. However, patients had risk factors for retinopathy, including longstanding diabetes of an average of about 13 years and a baseline hemoglobin A1c of about 8.7 percent.

As mentioned previously, trends in diabetic retinopathy endpoint did not favor liraglutide. The proportion of patients who had treatment with photocoagulation or intravitreal agents and vitreous hemorrhage was slightly higher for liraglutide than placebo, although there were few retinopathy events identified in the trial and differences were small.

While there was no evidence of benefit with the diabetic retinopathy endpoint, we have concerns regarding the components of this composite endpoint. First, the degree of retinopathy in each patient was not graded, and therefore changes in

the severity of retinopathy cannot be determined. Multiple factors influence whether a patient is treated with either retinal photocoagulation or intravitreal agents, including cost and local medical alternatives, thereby making this endpoint unreliable.

The onset of diabetes-related blindness occurs rarely and is difficult to judge whether the blindness is due to diabetic retinopathy. For example, the development of cataracts in a patient with diabetes may result in blindness. However, although diabetes-related, this event would not be a result of retinopathy. Also, the duration and severity of an episode of vitreous hemorrhage may have different clinical implications; however, this duration was not captured in the trial. Finally, the decreasing hemoglobin A1c in this trial may make the interpretation of retinopathy difficult, particularly in the first year of treatment.

The second component of the microvascular endpoint, nephropathy, was composed of two laboratory-based assessments, and two clinical

assessments. For the most part, EAC-confirmed nephropathy events tended to favor liraglutide over placebo with the exception of death due to renal disease. However, the nephropathy endpoint in LEADER was driven by the new onset persistent macroalbuminuria, which is not an established surrogate endpoint for renal benefit from a regulatory perspective.

In addition, 3 of the 4 components of the nephropathy endpoints could have been reversible. These components included the new onset of persistent macroalbuminuria and persistent doubling of serum creatinine. In our view, the definition of persistence was not well established in the EAC charter for both of these components.

Similarly, although the hemodialysis endpoint excluded acute reversible causes, there was no prespecified time period to define chronic dialysis. Therefore, the interpretation of this endpoint could still capture reversible events.

In addition, the definitions for renal death did not provide adjudicators' guidance on the

identification of patients who died due to renal disease. Review of the narratives with these events revealed concomitant illnesses, which clouded the interpretation of the cause of death.

In summary, the LEADER trial suggests that liraglutide is both non-inferior and superior to placebo on the 3-point MACE endpoint. The results are internally consistent for each of the components, and although not pre-stratified in a testing hierarchy, cardiovascular death was lower for liraglutide than placebo.

The subgroup analyses were generally consistent with the primary analyses, except for the U.S. versus non-U.S. in cardiovascular history subgroups. There was a low amount of missing data with about 3 percent of patients not completing the trial, and less than 1 percent of patients having no known vital status.

Lower systolic blood pressure, body weight, and hemoglobin A1c during the trial was observed for liraglutide over placebo, while heart rate and diastolic blood pressure trends favored placebo.

It is unclear whether differences in these variables affected the overall MACE findings. The mechanism by which liraglutide exerts a cardioprotective effect is also unknown.

Finally, there was no conclusive evidence that liraglutide has a long-term beneficial effect on microvascular outcomes although the trial was not primarily designed to demonstrate a benefit on these.

I will not turn the presentation over to Dr. Julie Golden to review the non-cardiovascular safety of LEADER.

FDA Presentation - Julie Golden

DR. GOLDEN: Good morning, chairman and committee members. My name is Julie Golden, and I am a clinical reviewer in the Division of Metabolism and Endocrinology Products. I will be presenting the non-cardiovascular, non-thyroid cancer portion of the LEADER safety review.

Here is a brief outline of my talk. I'll start with some of the regulatory history behind the safety issues of interest and how these were

assessed in LEADER. I'll take a brief detour to specifically discuss pancreatic safety with liraglutide and other GLP-1 receptor agonists. I'll then proceed to targeted safety issues from the LEADER trial focusing on non-thyroid neoplasms, gallstones and pancreatitis, and finally renal safety. Thyroid neoplasms are discussed in a separate presentation by Dr. Shannon Sullivan.

LEADER was designed to fulfill the postmarketing requirement to address liraglutide's cardiovascular safety. LEADER was also required to assess specific safety issues of interest. In addition to endpoints related to medullary thyroid carcinoma, that you will hear about in the next FDA presentation, the PMR also included the required assessments of pancreatitis, renal safety, serious hypoglycemia, immunologic reactions, and neoplasms.

In addition, a number of safety issues that were identified postmarketing were subsequently raised, including reports of severe pancreatitis and pancreatic cancer, as well as renal failure, all of which will be addressed in this talk.

In 2014, liraglutide for chronic weight management, or Saxenda, was discussed at an FDA advisory committee meeting and subsequently approved by FDA for U.S. marketing. Additional safety issues were raised in the Saxenda review, including an imbalance in breast cancer and gallstones. Both of these issues will be discussed today.

Before I get to the LEADER safety review, I want to briefly review the regulatory history surrounding pancreatic safety concerns for liraglutide and other drugs in the GLP-1 class.

In addition to small unfavorable imbalances in events of pancreatitis that were observed in some premarketing clinical trials of GLP-1 based drugs, postmarketing reports of severe pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis, resulted in inclusion of pancreatitis information in the warnings and precautions section of the product labels across the class.

Subsequent to the approval of liraglutide

and other drugs of this class, several investigators published papers hypothesizing a link between use of GLP-1 based drugs and pancreatic cancer. These investigators posited, largely based on animal data, that these products caused chronic pancreatic inflammation, which could then progress to pancreatic cancer.

To evaluate this concern, FDA examined available animal and clinical data for liraglutide and other GLP-1 drugs and conducted additional animal experiments. The FDA's assessment did not corroborate the published findings or establish the presence of a treatment-related effect on chronic pancreatic inflammation or pancreatic cancer.

Specifically, no pancreatitis was observed in healthy animals or in rodent models of type 2 diabetes. Furthermore, pancreatic cancer was not observed in dedicated, life-long rodent carcinogenicity studies.

Finally, the pre- and postmarketing clinical data available at the time, though limited, did not support the existence of an association between use

of GLP-1 drugs and pancreatic cancer.

To obtain additional information and further explore the existence of a potential relationship between use of GLP-1 receptor agonists, pancreatitis, and pancreatic cancer, FDA asks that these events be designated of special interest in randomized, controlled clinical trials such as LEADER.

The safety assessment in LEADER was focused on events associated with GLP-1 receptor agonists as a class, those associated with the complications of diabetes, and events raised specifically in reviews of liraglutide, both Victoza and Saxenda.

Only certain adverse events were systematically collected in LEADER: serious adverse events and those events prespecified as medical events of special interest. Furthermore, certain events were independently adjudicated by 1 of 4 designated event adjudication committees or EACs.

This table highlights some of the predefined medical events of special interest, and those

events that were additionally adjudicated by the EAC. Note that although nephropathy was considered a medical event of special interest, other renal safety issues may not have been. It would have been left to the investigator's discretion to report, for example, a renal adverse event that was not serious or did not meet one of the other criteria.

The first targeted safety issue I will discuss is neoplasms. Because small imbalances were observed in neoplasms overall in the premarketing trials for liraglutide, they were included as a safety issue for specific focus in the PMR and were identified as medical events of special interest in LEADER.

All potential neoplasms in this trial were sent to the neoplasm EAC for adjudication. These were typically sent by the investigator, who would identify a neoplasm event as a medical event of special interest. Events could also be identified through a search of the adverse event database or via the EAC itself while the members were reviewing

source documentation for another event.

In confirming a diagnosis, having pathology was of foremost importance. If pathology was not available, reports of extensive disease or markedly abnormal tumor markers could be considered. In addition to confirming the diagnosis, the EAC also classified the neoplasm by organ or tissue and by malignancy status.

This figure illustrates the neoplasm adjudication process and flow of events. The majority of events were identified by the investigator. Forty-two percent of the almost 3500 events sent to the EAC were confirmed, and they were fairly evenly split between liraglutide and placebo.

This table enumerates the proportions of patients on liraglutide and placebo with any neoplasm confirmed by the event adjudication committee; 6.3 percent of patients on liraglutide, and 6 percent of patients on placebo had a malignant neoplasm, as confirmed by the EAC.

This plot of malignant neoplasms by organ or

tissue shows that some hazard ratio point estimates favor liraglutide, some favor placebo, and overall, the distribution is fairly evenly balanced.

I will focus on a couple of specific malignant neoplasms of particular interest. The first I will discuss is pancreatic cancer. As seen in the figure, the point estimate is not in favor of liraglutide. This is of particular interest because of the historical concerns regarding pancreatic safety that I mentioned at the beginning of the talk.

Ductal adenocarcinoma of the pancreas, which is the most frequent type of exocrine pancreatic cancer, is an aggressive malignancy with a high mortality rate. It is most commonly diagnosed at an advanced stage and has a long latency between the first mutation and metastatic potential.

As seen in this table, the numbers of EAC-confirmed pancreatic neoplasms in this trial were relatively few, but an imbalance was noted driven by a higher proportion of patients on liraglutide with pancreatic malignancies.

Separately, a search of adverse events of malignant pancreatic neoplasms within the clinical database was conducted and identified events in the LEADER trial with the preferred terms listed here.

Utilizing this search, 11 patients on liraglutide and 10 patients on placebo had a pancreatic cancer adverse event reported. Given its discordance between EAC-confirmed events and events captured by the adverse events search, we consulted the FDA oncology division to review potential pancreatic cancer events. This consult review can be found in your briefing document. The FDA consultants considered events in 13 patients on liraglutide and 8 patients on placebo to be at least possible pancreatic adenocarcinoma.

To summarize, there are differences in the numbers of events reported by the investigators, those that were positively adjudicated and those considered at least possible by the FDA oncologists. We'll go through these in a bit more detail in the next few slides.

I have come up with a schematic to

illustrate the flow of events. Here are the patients with events identified by the investigators: liraglutide 11 and placebo 10. Thirteen patients on liraglutide and 5 on placebo had EAC-confirmed events. For liraglutide, all 11 investigator-reported events were EAC confirmed, as were 2 additional events with the preferred term pancreatic neoplasm. By contrast, only 5 of the 10 investigator-reported events in the placebo group were confirmed by the EAC.

One of these events not confirmed as pancreatic cancer was confirmed by the adjudication committee as a lymphoma. Four patients died due to the event without a pathology specimen available to make a diagnosis.

The FDA oncology division was asked to review the EAC-confirmed cases in addition to the 4 additional pancreatic cancer death cases. One of the EAC-confirmed cases in a liraglutide-treated patient was dismissed by the consultants as most likely intrahepatic cholangiocarcinoma. However, an additional cholangiocarcinoma case was

incidentally found to be associated with a pancreatic mass.

This event was considered by the FDA consultants as a possible pancreatic cancer case. Three of the pancreatic cancer deaths were considered possibly or probably pancreatic adenocarcinoma by our consultants, whereas one was thought to be most likely a neuroendocrine tumor.

These tables enumerate the FDA's consultants' assessment of these cases based on their assessment of likelihood of the diagnosis. Events in 9 liraglutide-treated patients versus 3 placebo-treated patients were considered by the FDA consultants as definite pancreatic adenocarcinoma, and all of these definite events were also EAC-confirmed.

Here are the lists of 13 liraglutide-treated patients and 8 placebo-treated patients identified by the FDA oncology consultants with at least a possible pancreatic cancer event during the trial. These are summarized in order of time in months to event from randomization with age, sex, and some of

the potential risk factors for pancreatic cancer, such as obesity, smoking, and history of pancreatitis included.

Nine of the 13 liraglutide treated patients were over age 65 at the time of diagnosis. Nine of the 13 patients had a baseline body mass index of 30 or greater. Seven of the 13 were previous or current smokers, and 1 patient had pancreatitis reported in her medical history at baseline.

Genetic or familial predictors of pancreatic cancer were either not reported or were negative. Most patients had at least one of these identified risk factors, and therefore it is very difficult from the available data to determine whether or not there is a potential drug relationship.

In summary, a small imbalance in pancreatic cancer was observed in this trial not in favor of liraglutide. Because of the small number of cases, it is unknown if this imbalance was observed due to an acceleration in the development on pancreatic cancer, due to treatment with liraglutide, other factors such as differences in patient risk factors

or ascertainment, or simply a chance finding.

The uncertainty regarding the case count decreases confidence somewhat in the findings. I will point out that our consultants only reviewed the previously shown 23 cases and did not re-adjudicate every single potential neoplasm, so these numbers may be underestimates.

Finally, at a median of 3.8 years, the duration of this trial is such that it cannot be conclusively determined whether long-term exposure to liraglutide increases the risk of pancreatic cancer.

Now I will turn my attention to breast cancer. As seen in this slide, the point estimate of the hazard ratio for breast cancer in this trial is very close to 1. We are discussing breast cancer in this trial because during the Saxenda review, a numeric imbalance not favoring liraglutide was observed in the clinical trials.

An ongoing 3-year Saxenda trial, as well as the LEADER trial, were utilized to further assess this potential risk as part of postmarketing

required studies for Saxenda. The results of both trials were reviewed by FDA's Division of Epidemiology, as seen in your briefing document.

As shown here, the 3-year Saxenda trial demonstrated a persistent imbalance in breast cancer events, although the numbers are small. Also note the 2 to 1 randomization in this trial.

In LEADER, by contrast, the events were fairly well-balanced with 21 women in the liraglutide arm and 20 women in the placebo arm developing malignant breast neoplasms.

In summary, a similar incidence in breast cancer was seen among treatment groups in the LEADER trial. Although a promoter effect seems unlikely based on these findings, the duration of LEADER is insufficient to draw conclusions whether long-term exposure to liraglutide increases the risk of breast cancer.

The next targeted safety issues I will discuss are gallbladder events and pancreatitis. Because these events are occasionally comorbid, I will discuss them together.

Liraglutide has been associated with acute pancreatitis in liraglutide diabetes trials and in postmarketing reports. Type 2 diabetes has also been considered a risk factor for acute pancreatitis in retrospective cohort studies.

In weight management trials of Saxenda, gallstone events and acute pancreatitis were observed more frequently in the liraglutide-treated patients versus placebo-treated patients. Only some of the acute pancreatitis events could be attributed to gallstones. Also, because gallstones were seen to a greater extent with liraglutide versus placebo for any given degree of weight loss in the clinical trials, it was thought that liraglutide may increase gallstone formation by a weight-loss dependent, or independent mechanism, or both.

Liraglutide is also associated with increases of lipase and amylase of uncertain clinical significance in the absence of other signs and symptoms of pancreatitis. In LEADER, more patients on liraglutide than placebo had elevations

in amylase and lipase with routine clinical testing, although the mean values remained in the normal range.

Investigators were instructed to report acute gallstone events as medical events of special interest. Therefore these events were systematically collected, although they weren't adjudicated. Events were identified for analysis from the clinical adverse event database using a predefined preferred term search.

Here are the results of acute gallstone disease events in LEADER based on the prespecified search, including the most common preferred terms contributing to the imbalance. The findings are consistent with previously described events observed with Saxenda; that is, a numerical increase in the number of events in the liraglutide group.

As noted on the previous slide, most events were due to cholelithiasis or cholecystitis, and the majority were serious adverse events. In terms of risk factors, more patients with acute gallstone

disease on placebo than liraglutide had a history of biliary disease reported at baseline.

The proportions of patients with obesity and female sex were generally similar among groups. There was no clear relationship between liraglutide-associated weight loss and development of a gallstone-related event.

Now I'll discuss acute pancreatitis. Investigators were instructed to report pancreatitis events as medical events of special interest, and in addition they were adjudicated by the pancreatitis subcommittee. An acute pancreatitis event was confirmed when 2 of the 3 were present: severe acute upper abdominal pain; pancreatic enzymes at least 3 times the upper limit of normal; or characteristic findings on imaging such as CT, MRI, or ultrasound. In addition, the EAC assessed the severity of the event.

This table presents the results of the acute pancreatitis events confirmed by the adjudication committee. As you can see, the results do not suggest a worse result for liraglutide, and perhaps

it even looks numerically favorable.

Here are some additional details regarding the EAC-confirmed acute pancreatitis events. Approximately one-third of liraglutide-treated patients with acute pancreatitis had gallstones confirmed by imaging at the time of the event.

Regarding risk factors, in general, similar proportions of patients with acute pancreatitis in each treatment group had obesity or hypertriglyceridemia at baseline. Alcohol history was not available for the majority of patients with pancreatitis in either group. Fewer patients with acute pancreatitis treated with liraglutide versus placebo had a history of pancreatitis or biliary disease. Those were the EAC-confirmed events.

Here is a listing of events that were sent to the Pancreatitis EAC for adjudication, but were not confirmed, presented by investigator reported preferred term. As you can see, more patients on liraglutide than placebo had pancreatitis events that were not confirmed. This includes a variety of preferred terms with varying degrees of

specificity for pancreatitis.

Small imbalances are noted for preferred terms of pancreatitis, acute pancreatitis, and chronic pancreatitis not in favor of liraglutide. One event of edematous pancreatitis that was not EAC-confirmed was reported in a placebo patient.

The sponsor reviewed the source documentation for 50 events in 43 liraglutide-treated patients and 21 events in 19 placebo-treated patients that were adjudicated for acute pancreatitis and ultimately not confirmed. The following was noted.

Thirty-nine percent of these non-confirmed events did not fulfill any of the diagnostic criteria for acute pancreatitis; that is, abdominal pain, enzymes, or imaging. Forty-five percent of events had documentation of elevations of pancreatic enzymes at least 3 times the upper limit of normal as the only criterion fulfilled, and 11 percent of events had documentation of abdominal pain as the only criterion fulfilled.

Also, only 54 percent of events reported in

both treatment groups had all 3 diagnostic parameters with information available in the source documentation.

I will mention a few examples of investigator-reported acute pancreatitis not EAC-confirmed in the liraglutide group just to demonstrate the complexities of some of these cases. The first patient I have listed is a 64-year-old female with a 20 year history of type 2 diabetes, chronic renal failure, and history of cholecystectomy among other medical problems. She presented with diarrhea; vomiting; mental status changes; acute and chronic renal failure; a blood sugar of 1200; and a lipase of 7900, which ultimately rose to a peak of 12,000. She had no complaint of abdominal pain, and the CT scan showed an enlargement of the head of the pancreas.

The second patient is also a 64-year-old female who presented with epigastric pain radiating to her back, nausea, severe hydronephrosis from a kidney stone, and renal insufficiency. The peak lipase was 761, which is less than 3 times the

upper limit of normal, and CT showed no obvious abnormalities in the pancreas.

The third patient was an 82-year-old female. A discharge summary from a hospitalization reported an event of acute pancreatitis and noted that a cholecystectomy was performed. However, no additional information was provided, such as laboratory data or imaging.

In summary, LEADER supports the previous finding with Saxenda that liraglutide is associated with gallstone-related events. Although liraglutide did not appear to increase the risk of adjudicator-confirmed pancreatitis, it's not clear that the results from this trial can dismiss the concerns of pancreatitis at this time. More pancreatitis events were not EAC-confirmed in patients treated with liraglutide. In some cases, it appears this may be due to the strict EAC definitions for pancreatitis.

Finally, as was reported with Saxenda, only a subset of pancreatitis events appeared to be associated with gallstones in this trial.

The last topic I will be discussing is renal safety. Although liraglutide has not been found to be directly nephrotoxic in animal studies or clinical trials, renal impairment has been described with GLP-1 receptor agonists associated with the known gastrointestinal adverse reactions of this drug class and consequent hypovolemia.

At the time of the original approval, this safety concern had emerged with another member of the class, and therefore a renal safety assessment was included as a part of the PMR for liraglutide. Labeling for liraglutide includes the warning about postmarketing reports of renal failure, as reproduced here. In LEADER, nephropathy was evaluated and adjudicated as an efficacy endpoint.

Although other renal adverse events were not specifically collected as medical events of special interest, a search of predefined acute renal failure terms was conducted from the adverse event database.

This table enumerates the four most common events identified by the predefined acute renal

failure search of serious adverse events and medical events of special interest. Overall, the proportions of events were similar among groups with a slight numerical imbalance in favor of liraglutide overall and by baseline renal impairment generally driven by fewer proteinuria events in the liraglutide group.

Similar proportions of patients in each group discontinued permanently due to events of acute renal failure. It was also noted that slightly more renal deaths were reported in patients in the liraglutide versus the placebo group.

Within the acute renal failure search, 18 patients on liraglutide and 14 on placebo had events reported as leading to death. A review of the liraglutide narratives indicated that most of these events occurred in the setting of renal complications of other conditions.

In addition, a slight numerical imbalance was noted in non-cardiovascular deaths classified post hoc by the EAC as renal, 11 versus 5. A

review of the liraglutide narratives indicated that most were related to worsening of chronic renal failure.

In summary, events of acute renal failure were similar among groups. There were fewer events of proteinuria in the liraglutide group, however, the clinical relevance of this is unclear. Differences in acute renal failure events between treatment groups were not observed with worsening baseline renal impairment. A slight imbalance in renal deaths not in favor of liraglutide was noted. There was no obvious contribution of liraglutide-related gastrointestinal adverse reactions to renal deaths.

That is the conclusion of my portion of the presentation. I will now turn the podium over to Dr. Shannon Sullivan, who will discuss thyroid cancer.

FDA Presentation - Shannon Sullivan

DR. SULLIVAN: Hello. I am Dr. Shannon Sullivan, medical officer with the Division of Metabolism and Endocrinology Products, and I will

be presenting the LEADER data related to medullary thyroid cancer or MTC.

Prior to marketing, liraglutide was shown to cause thyroid C-cell tumors in both sexes of mice and rats at clinically relevant exposures. Labels for all long-acting GLP-1 receptor agonists, including liraglutide, contained boxed warnings regarding risk of thyroid C-cell tumors.

Specifically, the Victoza label states "Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rodents. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma in humans, as human relevance could not be determined by clinical or non-clinical studies. Victoza is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2."

Two non-clinical, postmarketing requirements were mandated to better characterize the potential risks to thyroid health associated with liraglutide. The results of these studies are

available, and I will briefly discuss them here.

Based on the non-clinical PMR studies, long-term risk of thyroid C-cell tumor formation after transient exposure to liraglutide could not be excluded, based on studies in which mice were administered liraglutide for 25 percent of their lifespan, while C-cell hyperplasia, induced after 26 weeks of exposure to liraglutide, failed to resolve after a 78-week treatment free period in a few mice, and 1 mouse developed a C-cell adenoma. Study interpretation was confounded by unanticipated C-cell hyperplasia in control mice. Further, GLP-1 receptor dependence of rodent thyroid C-cell tumor formation was confirmed in studies in GLP-1 receptor knockout mice.

Finally, a roll of the rearranged during transfection, or RET, to proto-oncogene in rodent C-cell tumor formation was excluded. Due to the long latency of thyroid C-cell tumors induced by liraglutide in rodents, human relevance of thyroid C-cell tumors cannot be ruled out based on these non-clinical data.

I will now discuss MTC-related data from the LEADER trial. In LEADER, calcitonin values greater than or equal to the 20 nanograms per liter and thyroid neoplasms were prespecified medical events of special interest. These medical events of special interest were assessed by endocrinologists on the calcitonin monitoring committee and by endocrinologists and oncologists on the EAC, respectively.

Elevated serum calcitonin is a potential biochemical marker of C-cell hyperplasia. In LEADER, calcitonin levels greater than or equal to 20 were considered elevated. The serum calcitonin was measured fasting at baseline and every 12 months after the start of study drug using chemiluminescent immunometric assay in all participants. The lower limit of quantification for this assay was 2.0, and the upper limit of normal was 8.4 in men and 5.0 in women.

Thyroid neoplasms were classified as benign, premalignant, or malignant. Malignant neoplasms were further subtyped as either C-cell hyperplasia,

medullary microcarcinoma, medullary carcinoma, or other, based on cytology or pathology reports that were confirmed by the EAC and by a blinded external endocrinologist reviewer. Of note, all cases of other thyroid neoplasms in the LEADER trial were of papillary origin.

The proportion of patients with post baseline calcitonin levels greater than or equal to 20 at any study visit was similar between liraglutide and placebo-treated patients; 3.1 percent in the liraglutide group compared to 3.0 percent in the placebo group.

Regarding events of premalignant or malignant thyroid neoplasms, no subject randomized to liraglutide or placebo had an event of C-cell hyperplasia during the trial. One subject randomized to placebo had an event of medullary thyroid cancer, and no subject randomized to liraglutide had an event of MTC. Five subjects randomized to liraglutide had events of papillary thyroid cancer compared to 3 subjects randomized to placebo with papillary thyroid cancer.

To summarize data from the LEADER trial, elevations in serum calcitonin greater than or equal to 20 were seen equally as frequently in the liraglutide and placebo groups. Further, among LEADER participants, there were no excess events of thyroid neoplasm overall, of C-cell hyperplasia, or of medullary thyroid cancer in subjects randomized to liraglutide compared to those randomized to placebo.

Limitations to the LEADER thyroid cancer data include a small overall event rate for thyroid neoplasms during the trial; approximately 0.1 percent of subjects in both the liraglutide and placebo groups.

In addition, the median follow-up time for LEADER participants was 3.8 years, a relatively short period to observe new thyroid cancer events given the generally slow growing nature of thyroid malignancies.

The human risk of MTC is continuing to be evaluated in epidemiologic studies that are ongoing. For Victoza, postmarketing requirement

1583-7 established an MTC case series registry of at least 15 years duration. To satisfy this PMR, sponsors of all long-acting GLP-1 receptor agonists formed the MTC Registry Consortium and are using two approaches.

First, the consortium is monitoring annual trends of MTC in the U.S. To do so, they are collaborating with the North American Association of Central Cancer Registries with the objective of identifying any possible increase in MTC related to the introduction of long-acting GLP-1 receptor agonists into the U.S. market.

They are comparing age-adjusted incidence of MTC by year during a baseline period of 2001 to 2009, to years following the introduction of long-acting GLP-1 receptor agonists into the U.S. market, that is 2010 and beyond.

Second, the consortium has established a disease registry of incident cases of MTC in adults in the U.S. with the objective of characterizing medical histories and possible risk factors, including history of treatment with long-acting

GLP-1 receptor agonists.

After obtaining consent, the registry staff administer a questionnaire over the phone to capture a long-acting GLP-1 receptor agonist exposure in adults diagnosed with MTC. The MTC disease registry is ongoing, and the final report is due in 2026.

This concludes my presentation and the FDA's presentations for today. Thank you for your attention.

Clarifying Questions to FDA

DR. WILSON: Thank you very much. Now we're open for the advisory committee questions to the FDA.

DR. YANOVSKI: Hi. Sue Yanovski from NIH. I had a question about the other subgroup analysis imbalance we saw, which was the age over 60 and CVD risk factors, but not a preexisting history of cardiovascular disease.

This is a relatively lower risk group than the 3a criteria, but the sponsor also presented that meta-analysis from the phase 3 trials showing

that the point estimates for a relatively lower risk group were actually in favor of liraglutide versus in this group.

I'm wondering what else might be different between these groups. For example, I'd imagine the 3b group is older perhaps than the 3a group, and whether you looked at that as a potential factor.

DR. YANOFF: Hi. Lisa Yanoff, clinical team lead. I think that that subgroup analysis, we agree with what the applicant presented. You notice the confidence interval is very wide, and it was only 10 percent of events. If we assume it's real though, which we're not sure, what could have accounted for it.

We didn't look at age outside of the overall subgroup -- and as far as the meta-analysis goes from the original program, the methodology, the method of capture, was all questioned by the original EMDAC during the original approval of liraglutide.

As you're all aware, the guidance was implemented after most of their phase 3 studies had

been done, so we don't consider those entirely reliable, as reliable, for assessing MACE as we do for LEADER, given the retrospective nature of the event capture.

If you're looking for consistency between those two, it's not clear, one, that the subgroup is real, that the CV risk factors are real; and two, that the benefit was real in the pre-approval trials. So there's some uncertainty there that they haven't been able to explain.

DR. CONDARCO: If you also look at slide 19 in the FDA statistical analysis, there is a picture depicting the overall subgroup analysis for patients 65 or older or below 65. That gives you an idea a little bit of age, a little bit older patients in the LEADER trial and shows the overall hazard ratio for that subgroup favoring liraglutide.

Again, subgroup analyses, as you know, are exploratory. They're post hoc analyses in terms of exploring that particular subgroup a little bit further.

DR. GUETTIER: I just want to say one more thing about the two subgroups. I think the first subgroup actually had -- even though the applicant states that they're not -- they can't really be thought of established versus non-established, the first subgroup did have arterial stenosis and that was one of the categories, or they had a declared first event, atherosclerotic cardiovascular event, whether it be an MI or a stroke.

The first subgroup, where the bulk of the MACE events came from and the subgroup really driving the overall results, is akin to an established cardiovascular disease subgroup, whereas the other subgroup, the only risk factor was the ABI index of less than 0.9. Some of them could have had an MI maybe in the past. I'm not sure.

They would have probably been -- but to answer your question, we don't really know what the differences were, and we didn't really do comparative analysis between this and the premarketing demographics to see if they were

similar or different. We didn't do those analysis.

DR. WILSON: Dr. Wang?

DR. LOW WANG: Cecilia Low Wang. A question for Dr. Golden. Looking at your slides number 8 and 9, I didn't quite understand -- if you could clarify the difference between the EAC-confirmed index events in slide 8 versus slide 9. One is events and one is neoplasms, but I didn't quite understand the difference.

DR. GOLDEN: If we can advance actually the slides so that the figure pops up.

DR. LOW WANG: Go to the next --

DR. GOLDEN: Right, but there's a figure on slide 8 where -- and I don't know why it's not popping up, but where we're seeing events. So these are events, where as the next page on 9 are patients.

DR. LOW WANG: Oh, I see. Okay, so number of patients and number of events.

DR. GOLDEN: Exactly.

DR. LOW WANG: I see.

DR. WILSON: Dr. Burman?

DR. BURMAN: Thank you. Ken Burman. I'm not a statistician, but I did notice that the New England Journal had a letter to the editor at the end of last year on a LEADER trial pointing out that the power of the study to detect superiority was 75 percent, and that -- I'm not sure with FDA, but the general criteria is 90 percent. That was touched on briefly, but does the FDA have any comments on the power of the study to detect superiority?

DR. GUETTIER: I think that's a question maybe for the statisticians on the panel, how would they interpret power after the fact would be?

DR. HAMILTON: Well, we didn't really -- the study is powered for non-inferiority. And since it was such a large number of patients enrolled in the study, we didn't do any further investigation for superiority, but it should be powered for it.

DR. WILSON: Can we get a comment from you Dr. Neaton?

DR. NEATON: I didn't see the letter, Dr. Burman, but I would say focus right now on the

point estimate and the confidence interval around it as opposed to, a priori, what they thought power was going into it. At this point, we have the results and the confidence interval around the results, so that's what I would focus on.

DR. BURMAN: Thank you.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: Yves Rosenberg. Thank you. Going back to the primary efficacy analysis, both the sponsor and the FDA stated that the Cox model used for the primary analysis was adjusted for covariates, but I don't think I ever heard which covariates were used in the model.

Second, for the subgroup analyses, going back to my previous question earlier on, I didn't see how any of these subgroup analyses, like we saw insulin versus non-insulin or other important subgroups, were taking into account correlation and the influence of other variables. Thank you.

DR. HAMILTON: To answer your question, as far as the Cox model for the primary endpoint, treatment was the factor in the model --

DR. ROSENBERG: No other variables?

DR. HAMILTON: No other variables. They did do additional analysis looking at I believe age, sex -- I don't remember off the top of my head. There were various other variables that they did do, and the hazard ratios were still in line with what you saw for primary MACE.

DR. WILSON: Dr. Cho?

DR. CHO: Leslie Cho. I'm not really sure what non-confirmed events are. Does that mean that they were considered. The investigator said it was cancer, but there was no pathology, and that's why they're non-confirmed?

DR. GOLDEN: That's a good question. It was really a binary decision that the committee had to make, yes or no. The investigator, based on whatever data that he or she had at the time of the event, would report an adverse event. And if it was a neoplasm, for example, also reported as a medical event of special interest, that would flag it to go to the committee.

The committee had very specific criteria

that were used in order to ensure that the diagnoses were accurate or specific. And the sponsor had actually made the comment in their submission that the advantage of that is to increase specificity, but then you lose sensitivity.

So because of the strict definitions for both neoplasms and for pancreatitis, you might wind up with events that are not confirmed although the investigator might have reported them as such, if that makes sense?

DR. CHO: And are the non-confirmed events equal in both placebo and in the liraglutide, or is it different? Does the placebo arm have more events versus --

DR. GOLDEN: Dependent on the particular event of interest. For pancreatitis, there was a clear discordance between what the investigators were sending or what the EAC was seeing as terms of events that they needed to adjudicate.

For neoplasms, for the most part, the investigator-reported events were similar to the

EAC-confirmed events. So you wound up with a pretty good balance of these non-confirmed events between liraglutide and placebo, with the exception of those pancreatic cancer events that both I and the sponsor described. That's why we asked the consultant to provide some additional clinical expertise.

DR. CHO: Then my one final question is, in a subgroup analysis between the U.S. and non-U.S., is there a better granular data on the lipid-lowering drug differences between the U.S. and non-U.S., specifically more statin use in the U.S. population versus not?

DR. YANOFF: Could you clarify if you mean at baseline or --

DR. CHO: Yes, at baseline please; yes, at baseline.

DR. YANOFF: More granular than just lipid lowering, you would like the breakdown of statin versus other types of lipid-lowering therapy?

DR. CHO: There was data from other places and other trials where statin use is much higher in

the U.S. versus non-U.S. Fenofibrate use is different across the region.

DR. YANOFF: Statin was higher at baseline. The other ones may perhaps --

DR. CHO: In the U.S. versus non-U.S.?

DR. YANOFF: Yes, that's correct.

Alan, is that correct? Statin use was higher in the U.S. If you have the breakdown of the other products?

DR. MOSES: Well, I can show you again very briefly the -- not on our slides here, but statin use was definitely greater in the U.S. at baseline than in a non-U.S. population. That was also true of platelet-aggregating inhibitors. We do have a breakdown of the medications, and the biggest difference was actually in statins, but even for fibrates and others, there was a little bit higher use in the U.S. population.

DR. WILSON: If there are further questions, perhaps we'll come back to that after lunch or other questions? We had some others. Dr. Konstam?

DR. KONSTAM: I want to go back to the two

subgroups based on their entry criteria, that is established cardiovascular disease versus the risk. That really was the nature of the two groups, right? It wasn't that one was over 60 and one wasn't. It was one was a group with established disease, and one was a group that didn't have established disease, but they had some risk factors that the sponsor identified. So I just want to do a check with our FDA colleagues about whether I'm thinking right about this.

Subgroups are always hazardous to draw any conclusions from, and I certainly could not draw any conclusions from that particular subgroup. One subgroup is certainly much smaller than the other in terms of the events that contributed, so I don't think you could draw any conclusion from it. But I think it's highly relevant to what the labeling is going to be, I would think, for the indication.

Specifically, what the sponsor has on their slide is that they're talking about an indication for patients with type 2 diabetes and high cardiovascular risk. I think the evidence resides

in patients who have established cardiovascular or renal disease, mostly cardiovascular disease.

So I think that's where the relevance of those groupings come in; not drawing any different conclusion, but in terms of the labeling. Would that be right?

DR. YANOFF: Well, that's what we would like you all to discuss today. You're on the right track of what we're looking for, but we're not prepared right now to state where we want the labeling. We would like to hear that from you.

DR. KONSTAM: But that's where the discussion resides.

DR. YANOFF: Yes.

DR. KONSTAM: It's not trying to draw any other conclusion, I don't think.

DR. YANOFF: It's a discussion of the reliability of the subgroup. Exactly the way you laid it out, we'd like to hear from everybody, if you believe similarly or differently.

DR. WILSON: Dr. Budnitz?

CAPT BUDNITZ: Yes. Dan Budnitz. And on

this point just to clarify, from the clinical efficacy overview slides -- I guess slide 15 talked about the subgroup analysis and p-value interaction of 0.048 for U.S. versus non-U.S. I think I understand from the sponsor materials they did a similar test for interaction and got four I think subgroups. So maybe that's not U.S. but maybe U.S. and Canada together, and got 0.2. Obviously one is, by our traditional cutoff, statistically significant, positive test for interaction, and one is not; so if there could be some clarification of these different exact definitions of the subgroup being used, different models, or different tests for interaction.

DR. YANOFF: The original subgroup per region was the four components: North America, Europe, the rest of the world, and I think Latin America. That might be the p-value you're thinking of then -- Asia. Yes, thank you. And the p-value of 0.048 specifically came from the U.S. versus the rest of world.

CAPT BUDNITZ: U.S. versus rest of world.

DR. YANOFF: So U.S. versus non-U.S.

CAPT BUDNITZ: What is typically done, and what was prespecified? U.S. versus rest of world or --

DR. GUETTIER: So there were some prespecified subgroups that the sponsor had, prespecified, and I think regions was one of them. The one they showed was their prespecified subgroup. Internally and through guidance and statutes, we always look at U.S. subgroup, and in fact that's something we care about.

So it's almost a prespecified subgroup in our own shop. And whether or not they prespecify it, it doesn't matter to us because we'll always look at that subgroup when we're reviewing studies.

DR. WILSON: Dr. de Lemos?

DR. DE LEMOS: Yes, just a couple of questions for Dr. Hamilton. I noticed you presented a one-sided p-value as well for the primary efficacy analysis, and I'm wondering why, and should we be interpreting this differently? Because this afternoon, much of this is going to

come down to the strength of evidence for a single trial and whether it's compelling.

Second, I was also surprised that we didn't see any other additional analyses, indirect Bayesian analyses, or something that would get at the confidence in this result as a stand-alone result relative to suppositions about other drugs in the class or even the limited meta-analysis beforehand. And hoping you can help us a little bit, if you did other analyses, and how we should interpret the p-value, one or two-sided?

DR. HAMILTON: Well, here with the non-inferiority margin, the one-sided p-value is because we're just looking to rule out that 30 percent risk.

DR. DE LEMOS: I'm referring specifically to the superiority analysis, because I don't think that's going to be a major issue for us, non-inferiority. It's going to come down to establishing whether a single trial provides the level of evidence for a CVD superiority claim.

DR. WANG: Hi. This is Yun Wang, acting

stat team leader, Office of Biostatistics, FDA. As for why we use one-sided p-values instead of two-sided because we are interested in superiority, specifically here. That means we want to rule out that liraglutide is better than the placebo. That's why we use one-sided.

DR. WILSON: Dr. Konstam, you had a comment?

DR. KONSTAM: I love Jim's opinion about this. We're really used to looking at two-sided p-values. In just about every other NDA I can think of where this discussion has come up about, we're going to look at one trial, so the p-value is relevant. So whether we think that that's legitimate or not, it seems to me the standard approach for superiority has always been to look at two-sided p-values, and that's what I'm used to looking at. It seems to me that's the standard that I'd want to apply because that's what I've always been looking at up until now.

DR. DE LEMOS: Right, because we're talking about a two-sided p-value that's 0.011 --

DR. KONSTAM: Right.

DR. DE LEMOS: -- which is a -- and then, what about the other question? Did you all do any other analyses besides the simple --

DR. HAMILTON: We did not do any of the Bayesian analysis, no.

DR. GUETTIER: Could you clarify the types of analyses that you would have suggested done?

DR. DE LEMOS: I'm asking; I'm not suggesting. I'm just wondering, given the importance of -- this is going to be a very borderline question -- the result's are going to be probably borderline. Considering assumptions of neutrality versus data from the -- it would be interesting to know where our confidence is relative to the preliminary data from the analysis and even the data for other compounds in this class; assuming that that was a real result, where this puts us. Obviously, we'll look to you all for what you consider compelling evidence a little bit more this afternoon.

DR. WANG: I would like to clarify one question, one thing, why we did not do those

analyses. Because when we use meta-analysis or Bayesian analysis, it really depends on the design of the study we refer to. All those analyses are exploratory, so that's why we did not do it, and we did not present it. Thank you.

DR. WILSON: Peter Wilson. I have a question, too. I believe it would go probably to Dr. Condarco. I was curious whether you have any similar subgroup analyses at the lower glucose levels while on treatment, particularly individuals who were on medications that might cause hypoglycemia, whether there's an adverse signal in terms of safety.

This is related to Dr. Konstam's. It's not necessarily on the treatment group in comparison to the usual care group. The issue was low blood sugar. Is this harmful in this trial? Was it picked up for either arms of the treatments?

DR. CONDARCO: We didn't perform a subgroup MACE analysis evaluating patients who experienced severe hypoglycemia. I don't know if maybe the sponsor has performed that analysis.

DR. GUETTIER: Are you looking to delineate the influence of severe hypoglycemia on the MACE effects, so the endpoints of a post-randomization there?

DR. WILSON: Any information would be helpful. All of us in endocrinology and cardiovascular disease have the legacy of the ACCORD trial, and I was wondering whether they've done any of these types of analyses to sort out whether hypoglycemia is causing adverse in either arm of the trial.

DR. GUETTIER: Internally, at least at the FDA we didn't analyze what the post-randomization effects were for hypoglycemia on the MACE endpoints. Those analyses, from my understanding, can be technically difficult to perform, so I don't know if the applicant has done any analyses to evaluate that.

DR. MOSES: We have, Dr. Wilson, and we've done it in two different ways. I'm not sure if I can get the slide up because we have to switch systems here. But the bottom line to your question

about severe hypoglycemia affect the hazard ratio, the answer is it does not. It still favors liraglutide versus placebo.

We've also looked, separate from this and I'm sure probably beyond discussion, at the impact of severe hypoglycemia on outcomes overall, but not MACE.

DR. WILSON: I think we're trying to bring up the slide you mentioned.

DR. MOSES: This is the slide I mentioned. At the bottom, you see a post hoc analysis of severe hypoglycemia, yes/no, and the hazard ratio. Yes is the bottom of the two rows compared to the primary analysis.

DR. WILSON: Before we break, do we have any comments or questions from those on the phone? Because we're ready to take a lunch break.

DR. KEWALRAMANI: No comments from me.

DR. WILSON: Any others? Okay.

DR. OAKES: This is David Oakes, just a brief comment. I would imagine that any sort of Bayesian analysis that was referred to would

probably lead to a conclusion that the U.S. hazard ratio was numerically less than 1, but with a confidence interval that might extend beyond unity. Whether that's useful or not, I don't know.

DR. WILSON: If you would say that question again a little louder. We had trouble hearing you. It was about Bayesian analysis, but we didn't get all of it.

DR. OAKES: I'm guessing that if you did that Bayesian analysis, which took a mixture of a model of which there was no difference between U.S. and non-U.S. and a model in which the difference was stated explicitly, then you would get a hazard ratio still less than 1 for U.S. but with a confidence interval that would include the value 1.

I want to emphasize I haven't done this. I'm just guessing that that is what would happen.

DR. WILSON: Okay. So we're going to take a break for lunch. We'll be back at 1:05, and we have a couple of other questions to come.

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

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

(1:06 p.m.)

Open Public Hearing

DR. WILSON: Good afternoon. We're going to have an open public hearing session, and I have introductory remarks before our first speakers will go forward.

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, the 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 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 on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

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

Now we have several speakers, and each speaker has been given recommendations to speak

4 minutes. And if they speak longer than that, we will remind them to wrap up their comments.

Speaker number 1, will you come to the podium, introduce yourself, state your name and any organization you are representing for the record. Thank you.

MS. CLOSE: Good afternoon. My name is Kelly Close. I'm the founder of The diaTribe Foundation, which is a diabetes patient advocacy group formed in 2013 to help improve the lives of people with diabetes and with obesity. By way of disclosure, I also founded and help lead Close Concerns, which is a healthcare information organization that chronicles diabetes scientific and progress globally.

I was also cofounder of the diabetes market research firm, dQ&A, and my colleagues are actually going to review the disclosures of Close Concerns and dQ&A this hour.

I wanted to also say I've learned a lot since I first started coming to these hearings. I think my first one was for muraglitazar. I've

learned a lot about globally, the voices of patients and how much they're heard and not heard in professional organizations, and I just want to salute the FDA for giving us this chance to be able to try to connect with you.

I also just want to step back and say, the morning, it was a pretty intense morning. I also just want to encourage everyone to hopefully not lose the forest for the trees.

My first thing that I want to talk about is mean sentiment. So mean sentiment, that's how I'm trying to talk about statistics like all of you, right? My mean sentiment after this morning is just thanks because I think FDA is incredibly under-resourced. I'm not sure the world really knows about that. And as we look at all of the work that you do on behalf of patients to bring us therapies that are safe and effective and innovative, we really want to give you huge credit for that. So all of our appreciation.

Second, I just want to say that, again, after having come to these meetings for years and

years and years, we feel strongly that a lot needs to be done in terms of helping the community in terms of getting researchers and clinicians and patients all on one page, and we do need the tools to help us do so. There's a lot to be done there in translating research and in helping both clinicians and patients feel more successful and engaged.

The third thing is just to let you know, these results -- I hope you know this, but from patient perspectives all over the world, these are really big deals. I remember when I first saw these results and I remember looking at them on my iPhone, and I was in bed, and then shaking my husband, like "Look at what has happened."

I ran into -- my three kids share a room, and I told them what could happen for people with diabetes who are at really high risk of cardiovascular disease, and I was just weeping. Lola, the middle one, was like, "Why is mommy crying"?

But I mean you're in this. You can help

this happen. You can help us reduce this massive burden. We all know, obviously, type 2 diabetes and cardiovascular disease are inextricably linked. We know that, but in order to actually get to the point where patients are doing better globally, this does start with you.

We know that you've helped bring more therapies to market that are smarter and better, and many of them have reduced hypoglycemia and reduced weight gain and all of that. We're so grateful for that. But we also know that this means that the cardiovascular burden for our planet is much bigger. And so I really would love if you would keep that in mind.

I think that if you can think seriously about improving this label, this will also improve the awareness and discussions that patients have with their doctors. And we know that when people are more conscious about CV risk, that can only be a good thing. Having a proven therapy to turn to in combination with great access, which is also key, and with advice about healthy living -- and by

the way, doctors and nurses are going to have more time with this, Victoza, because there's less hypo and less weight gain, et cetera. That can empower clinicians, and it can empower patients, and we need to make sure that that happens.

Finally, I just want to say in my last few seconds, value-based healthcare is still a thing of the future, but it is the direction that we're heading. Taking a drug with a goal of prevention, that's not something that patients globally are used to, but if any drug can claim on its label that it reduces risk of cardiovascular events, that's a really big step.

With the availability of drugs able to reduce CV risk with value-based healthcare, healthcare systems could begin to think about prevention, and that could motivate them to reorganize around a value-based framework. There's so many compelling things that could make this happen, and I so hope that this happens on FDA's watch.

Thank you again for your leadership and

concern for multiple patient perspectives and for thinking beyond A1c, including important cardiovascular outcomes.

DR. WILSON: Thank you very much. Will speaker 2 go to the podium, introduce yourself, and state name, organization you may be representing.

DR. PRATLEY: Thank you very much, Mr. Chairman, committee members, FDA scientists and staff members, and other guests. My name is Richard Pratley. I'm from Florida Hospital in Orlando. Thanks for the opportunity to provide my independent perspective here.

I want to point out that I have worked with the sponsor over the last seven years on the LEADER study and other studies as well, and that the sponsor reimburses my hospital for travel as well as my time. I, however, don't receive any direct financial reimbursement from this activity or from any of my work with pharma.

I serve as co-director of the Florida Hospital Diabetes Institute. I also am the program head of the diabetes program at the Translational

Research Institute, so my perspective is one of both a clinician and a clinical researcher.

I also served as the global expert panel co-chair for the LEADER study. This was a group of investigators from around the world who provided significant input into the design, as well as the execution of the LEADER study.

Importantly, the global expert panel was intent upon making sure that the study population was clinically relevant and that during the trial they were treated to the best possible prevailing local standards.

During the trial, we met as a group. We provided input to the steering committee and to the sponsor. We monitored the progress of the trial, and in addition, we took feedback back to our respective countries. You've already seen that the CV risk factors were well-treated in the LEADER study, by and large, and that importantly, glycemic control improved during the trial. This is in large part due to the good work of all the investigators around the world.

Thus, the LEADER study enrolled a clinically relevant population, and it was conducted to the very highest standards. As a clinician then, I have a lot of confidence in the results of the LEADER study.

I started the diabetes journey almost 30 years ago, and a lot has happened since then. There's been a four-fold increase in the prevalence of diabetes since I started. We have 12 different classes of medications now, whereas we used to have two for the treatment of diabetes, and we've seen some remarkable progress with respect to cardiovascular disease in the general population. We've seen decreases in the incidence and prevalence of cardiovascular disease.

Unfortunately, patients with diabetes have not kept up with this progress. Cardiovascular disease is still a leading cause of morbidity and mortality in patients with diabetes, and I see this every day that I'm in clinic. Despite treating patients with statins and antihypertensives, they still progress to having interventions and

cardiovascular events. Thus, we need new treatments. We need new tools in the clinic in order to reduce the cardiovascular burden for our patients.

We've now entered a totally new era in diabetes management. It's an exciting time where we have these CVOTs that have demonstrated, in some cases, a cardiovascular benefit. In some cases, they haven't proven to have a cardiovascular benefit. The importance of this is this allows us to make reasonable choices for our patients to improve outcomes in the clinic.

The LEADER study was a large robust trial. I use that on a daily basis in clinic in order to provide the best possible care for my patients. We're also seeing improvements -- or changes in the advice from organizations such as the ADA about how to incorporate this new evidence into trial. And I therefore strongly urge you to consider revising the label for liraglutide to take into account this new and important evidence. Thank you very much.

DR. WILSON: Thank you very much. We're now

ready for speaker number 3. Please introduce yourself, state your name and any organization.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today. My name is Dr. Stephanie Fox-Rawlings from the National Center for Health Research. Our center analyzes scientific and medical data to provide objective health information to patients, providers, and policy makers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

Two of the major questions being addressed today relate to whether the LEADER trial provides sufficient evidence that the drug, one, does not increase cardiovascular risk, and two, is protective against this risk. Let's start with the second question since it is easier.

To say that it lowers risk, Victoza would need to demonstrate both a statistical and clinical improvement over placebo. In addition, the trial that provides support needs to be generalizable to the population of patients that are likely to

consider using the product.

In the LEADER trial, the drug shows a small improvement, but it is not clear that this reduction in risk is clinically relevant. The incidence of a cardiovascular event was reduced from 3.9 events per hundred patient-years, to 3.4 events.

Even more important, the time to MACE is worse for the drug among U.S. patients than for patients in other countries. Since the FDA is a U.S. agency, it needs evidence that the drug decreases the risk of MACE in U.S. patients. Improvement in that risk needs to be established in a future study of U.S. patients.

Let's go back to the first question. Has the sponsor demonstrated that the drug does not increase cardiovascular risk? In the LEADER trial, the drug does not worsen the time to first MACE or increase the number of events compared to placebo. In fact, the hazard ratio for time to first MACE was statistically better than placebo overall, but it is worse for U.S. patients.

Even in the U.S., the hazard ratio was not statistically different for the drug and placebo. Therefore, within the confines of the trial, the drug does not increase risk and may reduce risk.

I want to quickly summarize concerns about the LEADER trial and why we aren't fully confident of the results. While the LEADER trial included over 9,000 patients who were exposed for at least 3 and a half years and was well-controlled, it isn't clear that the single trial was generalizable to all U.S. patients with type 2 diabetes and a high risk for cardiovascular events.

First, the differences are small, which may not be replicated in another trial. Second, there were more than twice the number of MACE events than predicted, which could suggest that there is something different about the patients that may not represent patients with type 2 diabetes with cardiovascular risks. Third, patients in the U.S. stopped taking both the placebo and drug to a greater extent and more quickly than patients in other countries.

What were the difference between the U.S. and other countries to cause this discontinuation rate, and were there differences in adverse events in the U.S. compared to elsewhere? Were there other reasons why the U.S. were not compliant?

The differences in the number of patients stopping treatment may have contributed to the fact that in the U.S., the time to first MACE was better for patients on the placebo than the drug, but it's impossible to know for sure.

In summary, there are questions relating to the LEADER trial that raises questions about its generalizability. With only one study, however large, we don't if the results would be replicated. The LEADER study suggests that the drug does not significantly increase cardiovascular risk. However, the sponsor has not demonstrated that it reduces cardiovascular risk, especially not for U.S. patients whose BMI, diet, and exercise habits might be quite different from those in other countries. Thank you.

DR. WILSON: Thank you. Speaker number 4

introduce yourself and state any organization you are representing.

DR. ALMASHAT: Thank you. My name is Sammy Almashat. I'm a physician and researcher with Public Citizen's Health Research Group, and I have no conflicts of interests.

The presentation today concerns the distinction between U.S. and non-U.S. sites and the strikingly different outcomes for those patients. We would ask that the advisory committee members take three points into account when they vote on today's approval decision.

Number one, this is a single trial as pointed out by the previous speaker. In almost all cases, the FDA does require two trials, one of which is confirmatory, to approve a drug, especially on a very clinically relevant indication such as this.

Number two, this drug is being approved for U.S. patients, and it is unknown to what extent the U.S. patients differ in terms of this outcome on this medication from non-U.S. patients.

Number three, in the United States, almost all drug approvals are approved based on intention-to-treat analyses. We are very concerned that the intention-to-treat analyses showed these strikingly different results.

The overall reduction in risk of MACE, cardiovascular death, and overall death with Victoza was due entirely to outcomes at clinical sites outside of the U.S. Before I get into that, it was disturbing to us that the FDA offered no explanation or no opinion on this subgroup discrepancy in their briefing document, nor did it weigh in on the company's post hoc explanation.

This is unlikely due to chance to us for several reasons. Number one, the difference for the U.S. subgroup was seen on multiple outcomes. Number two, there was the absence of even a trend on any of these outcomes for U.S. patients in favor of Victoza.

Number three, we should remember that 2500 U.S. subjects were enrolled, most of whom were at high risk for the outcome of interest and followed

for a minimum of 3.5 years. So in almost 9,000 patient-years of follow-up, there was an absence even of a trend in the intention-to-treat analyses in favor of Victoza.

The company relied on a post hoc analysis to explain the prespecified subgroup analysis. Again, the regional subgroup comparison was a prespecified per protocol analysis, and the company's explanation to explain the intention-to-treat discrepancy was a post hoc analysis. Again, when you're looking at the standards for drug approval, that's a very concerning standard by which to approve a drug for an indication such as this.

The fact remains that Victoza had no cardiovascular or mortality benefit for U.S. subjects in the more appropriate for real-world use intention-to-treat analysis. In such a scenario, there are two possible interpretations.

If the lack of benefit in U.S. subjects is not generalizable to the U.S. target population, then there are no data on which to base approval of Victoza in U.S. patients. If the data are

generalizable, then Victoza has been shown to be ineffective, at least in this one trial, on an intention-to-treat basis in U.S. patients.

That such a lack of efficacy was seen in a clinical trial setting in which subjects were carefully followed and assisted in their treatment, and for whom the treatment was free, makes it highly likely that American patients in a real-world setting will experience a similar or greater lack of cardiovascular benefit as a whole.

In summary, Victoza has not been proven effective for cardiovascular risk reduction in the U.S. population in which it was studied, going by the metric used for every other drug, which is an intention-to-treat analysis, in 9,000 patient-years of follow-up in mostly high-risk patients.

The absence of any evidence for a benefit in favor of Victoza on any of the three major outcomes raises serious doubts about the real-world effectiveness of Victoza for reducing cardiovascular risk in U.S. diabetes patients.

Given this lack of evidence of benefit in

U.S. patients, voting for approval, to us, for a cardiovascular benefit in the same patients, seems to us not to be rational. Thank you.

DR. WILSON: Thank you very much. Our next speaker is speaker number 5. Please introduce yourself and any organization you represent.

DR. WARREN: Thank you. My name is Dr. Mark Warren. I'm a practicing endocrinologist in Greenville, North Carolina. My travel expenses were paid for by the sponsor, Novo Nordisk.

I was a principal investigator in the LEADER trial, and I also served on the Global Expert Panel along with Dr. Pratley. The Global Expert Panel was formed by Novo Nordisk to help oversee this large global trial. It consisted of experts throughout the world from each country. We met several times a year to review the status of the trial and to address the issues that were identified.

We dealt with multiple issues such as recruitment, glycemic control, concomitant medications, standards of care, adherence to

investigational product. We also stressed the importance of retention in the studies.

The recommendations were disseminated to the national expert panels and the individual sites and investigators. This is the first CVOT for Novo Nordisk, and the largest study that they've done. The strategy helped ensure successful completion of the LEADER trial and gave confidence in its results.

The effectiveness of the strategy was evidenced by the high rate of completers in the trial, 96.8 percent, and by the fact that only 29 patients were lost to follow-up, which is unprecedented for such a large trial.

GLP-1 manifolds cardiovascular effects, and the expectations of CVOTs have been with high with GLP-1 receptor agonists. Yet with the ELIXA trial, we did not see any benefit, but fortunately a year later we did see this with the LEADER trial.

My main job every day is to take care of patients. It's to improve the lives of my patients with diabetes. Until we had results from the

EMPA-REG trial, we had no evidence of which medications we could use to improve cardiovascular risk. Now we have data for liraglutide as well.

As a clinician, I now have the evidence to select the proper drug for my patients, not only to improve glycemic control, but also to decrease cardiovascular events. Diabetes is a metabolic disease; not just a disease of hypoglycemia. We've known for 24 years that glycemic control improves microvascular disease and complications. But now we have data that with liraglutide, we can also save lives, as well as weight loss and low rates of hypoglycemia. LEADER was a well-executed trial I've seen from firsthand experience.

Allowing cardiovascular prevention on the label will provide direction to the healthcare providers to help use liraglutide to appropriate patients at high risk for cardiovascular events. On behalf of my patients who participated in the trial, I urge you, the committee, to recommend approval for this indication. Thank you.

DR. WILSON: Thank you very much. Speaker

number 6, please introduce yourself and any organization you represent.

DR. CHILTON: Thank you for inviting me. Bob Chilton, University of Texas. I'm director of the Interventional Laboratories in cardiovascular proteonomics. I found it most interesting because of all the things, I've never really worked with Novo Nordisk on this, so I'm clearly off the record. They sent me a plane ticket, and I came up.

I have studied this type of compound for over 25 years, and my interest is actually improvement of patient care. I live in San Antonio, and 80 percent of my cath patients have diabetes. Frequently, I can't even get a catheter in them. We have to use their arms.

You have a drug up her that has the ability to lose weight. At the same time, it actually shows a benefit for cardiovascular effects. A cardiovascular drug to me that has hypoglycemic effects, that would really be helpful to me in San Antonio.

The patients getting off a table primarily want to lose weight because most of them exceed my table weights, which used to be 300 pounds. Now they're 460 pound tables. This drug would allow somebody, for the first time in diabetes, to really have a weight-reducing drug; plus the fact you've got other benefits like blood pressure reduction, and you've actually got a cardiovascular death improvement.

We have EMPA-REG that was just published recently. It also has now the very first cardiovascular drug in diabetes to decrease cardiovascular death. I think this one stands very similar to that, but it has the advantage of weight loss and global risk reduction that we do not have with the other compound.

This would certainly improve the armamentarium of cardiologists that take care of diabetes patients to actually make them feel better, live longer, and have a much more productive life. And for many of them who are really overweight, this would give them a way to

start with having not to use as much insulin. Insulin, my patients gain weight. They don't lose it. This would potentially be something that would augment that way ahead of the schedule.

So from the time I started practice, this is the very first type of drugs that I've seen that actually change and actually drive clinical events in the right direction for diabetes. It's not glucocentric any longer. I think it's cardiovascular driven. Thank you.

DR. WILSON: Thank you. Speaker number 7, please introduce yourself and any organization you represent.

DR. SHAMALI: Good afternoon, Mr. Chairman, members of the committee, and FDA staff. My name is Dr. Mansur Shamali. I'm a practicing endocrinologist 20 miles north at MedStar Union Memorial Hospital. I don't have financial interests with the sponsor or their competitors, but I did serve as an investigator for the phase 3 trials for Victoza and the LEADER study.

But I didn't come to talk about my

experience as an investigator or the data or the statistics. I'm a very busy clinician who sees lots of patients with type 2 diabetes, and I wanted to share my experience with the high cardiovascular risk patients for whom I prescribe this medication.

The number one issue that I face with my patients is cardiovascular disease. Most of the patients are typically overweight or obese. They have comorbidities like hypertension, dyslipidemia, obstructive sleep apnea. They have often been smokers or are current smokers. And I'm struggling in my practice to help treat those patients and improve their cardiovascular risk.

One of my patients from two weeks ago, I'll call him Mr. Jones, he came to see me. He was recently discharged from a rehab admission after a pretty significant disabling CVA. His A1c was approximately 9 percent. His blood glucose readings were over 200 milligrams per deciliter. For the first time, I really felt confident that when I prescribe a medication, I'm actually going to be helping him and not just lowering the numbers

and treating the blood glucose and lowering the A1c.

Not only that, but I know that his risk of hypoglycemia would be relatively low with this medication, as well as the expectation of modest weight loss and modest improvements in blood pressure.

At my hospital, we have a pretty busy cardiac surgery service. I'm often called in to the hospital to see the diabetes patients who've had cardiac surgery. So I saw Mrs. Smith, not her real name, a very pleasant, centrally obese, 62-year-old woman. We needed to use both basal and rapid-acting insulin to control her diabetes after her surgery, and I was quite, frankly, concerned that she wouldn't be able to do that when going home.

Our decision to use liraglutide was, in fact, partly based on that it's so simple. It's a once-a-day injection. It eliminated the need for multiple insulin injections. She had had experience with Metformin and sulfonylureas in her

medical history, and not only had high blood glucoses, but also had pretty significant hypoglycemia, which in my view wouldn't be a safe thing following cardiac surgery..

So given her risk and given her previous medical history, having confidence in using a drug that has been shown to be safe for patients with high cardiovascular risk and potentially beneficial, it was extremely helpful to have that in my toolbox.

In conclusion, it's been very rewarding for me to help patients like Mr. Jones and Mrs. Smith and countless others. I'm delighted to be able to offer them medications that have superior safety and efficacy much more than the older agents, I believe.

I hope that the vote that the committee makes today has the potential to highlight these favorable cardiovascular risk issues because I think, as my previous colleagues have expressed, that we're trying to pick drugs that not only lower a number like A1c or blood glucose, but also are

safe and effective for our patients and can potentially promote longevity as well as improved quality of life. Thank you.

DR. WILSON: Thank you. Speaker number 8, please introduce yourself and any organization you represent.

MR. COLE: Okay. I want to thank the members of the committee for allowing me to give testimony today. Also, I would like to say that in accordance with their company policy, Novo Nordisk has paid for my travel expenses to attend today's committee meeting.

I would like to thank you for allowing me to testify today regarding my experience in being a participant in the LEADER trial for liraglutide. My name, again, is Vincent Cole, Sr. I live in Philadelphia. I participated in the trial at Thomas Jefferson Hospital from January of 2012 to October of 2015.

Initially, I did not want to participate in the study because I thought it was too long, four to five years. Another reason was because

liraglutide was an injectable medication, and that was a true challenge for me because I do not like injections. So I discussed it with my primary physician and my wife and consented to be part of the trial.

I began taking injections at bedtime, first at 6 units, then 12, and finally at 18 through the end of the study. In case you think my fear of needles had vanished, it had not. So in the 3-plus years that I was in the survey, my wife gave me my evening injection.

Every morning, I would take my fasting sugar levels and put them in a log. When I went to the Diabetes Research Center at Jefferson, it started off with frequent visits monthly, and then quickly went to quarterly visits. Connie Pepe and Dora Posey were very detailed and thorough as they collected the information from the study; took my blood and supplied me with the medication and supplies for the study.

After the study was over, these are the benefits that I saw from being in the study.

Liraglutide was easy to take. It was one pen with 10 doses. All I had to do was dial it up and take the shot. It helped me reduce my A1c from 9 to 7. It also helped me to lose some weight, over 20 pounds during the course of the study.

The participation in the trial helped me to establish routines for taking my medications, for my fasting sugars, for eating, and logging all of the information about what I ate, for logging my exercises, and for taking all of my medication at the same time. In addition to that, it helped me to schedule my maintenance visits for my physical exams, eyes, feet, and teeth.

I've been dealing with diabetes and high blood pressure for over 30 years, and I had developed some bad habits. But it wasn't until one day, about 20 years ago, I experienced an episode of double vision while I was driving on the highway, and this made diabetes real in my life.

I started to look at my family history. My son, Vincent Jr., he is a type 1 diabetic. My father was type 2. My mother and my aunt both had

aneurysms, and another aunt died from a stroke. These are cardiovascular events in my family history that concern me about my family's future and myself.

So if I were asked if I feel like I benefited from the liraglutide study, I would say yes. If I were asked if I would take liraglutide again, I would also say yes, but hopefully in oral form.

(Laughter.)

MR. COLE: In closing, I would like to say today that one of my church members also takes Victoza, and her A1c and weight are coming down. I believe that I was fortunate in being able to participate in this trial, and I am grateful to the many managers and staff at Novo Nordisk for bringing this medication to the marketplace. Thank you again for allowing me to testify.

DR. WILSON: Thank you. Speaker number 9, please introduce yourself and any organization you represent.

DR. LEFFERT: Thank you, Mr. Chairman, and

members of the committee. I am Dr. Jonathan Leffert, and I'm a practicing clinical endocrinologist in Dallas, Texas. I am the president of the American Association of Clinical Endocrinologists, and I'm making a statement on behalf of the organization. I would like to disclose that AACE receives grant funding from many pharmaceutical companies, including today's sponsor.

AACE is the largest organization of clinical endocrinologists in the world. We have over 7,000 members in 97 countries. Our mission is to enhance our members' ability to provide the highest quality of patient care.

It is well known that type 2 diabetes confers the highest lifetime risk for coronary heart disease of any single risk factor. This slide from the Framingham study data shows that men and women with type 2 diabetes at 50, free of coronary heart disease at that time, had about a 70 percent risk of coronary disease at age 70 for men and almost a 60 percent risk for coronary

disease at age 70 for women.

This epidemiological data clearly identifies the significant risk that type 2 diabetes confers on coronary disease, the leading cause of death in the United States.

The LEADER trial, as we've heard today, was a cardiovascular outcome trial to determine if liraglutide did not result in increased cardiovascular risk, a requirement of all diabetes drugs since 2008. This meeting of EMDAC is intended to consider a new indication for liraglutide to decrease cardiovascular risk in patients with type 2 diabetes. To date, only one antidiabetes drug, empagliflozin, an SGLT-2 inhibitor, has been given an indication to decrease CV risk based upon the EMPA-REG trial.

The primary endpoint typical of all CVOTs was MACE and showed a 13 percent decrease that compared to placebo. In addition, there were several supportive secondary endpoints. Overall, the risk of CV death was reduced by 22 percent.

The question arises is whether the GLP-1

receptor agonist, as a class, decrease CV risk, or is this a unique feature of liraglutide. At present, two other agents, exenatide extended release, in preliminary topline data reported by Astra Zeneca, showed non-inferiority compared to placebo. And in published data, exenatide showed CV safety, but no benefit in comparison to placebo.

From the clinical perspective, if approved for the indication of CV risk reduction, should all patients with type 2 diabetes be considered candidates for liraglutide? First, it always depends on the needs of the patient therapeutically. All medications are not appropriate for all patients.

To help in guiding physicians through the current medication options for type 2 diabetes, AACE publishes a yearly updated algorithm for comprehensive diabetes management, available on our website and a free downloadable app for your smartphone. Approval for this new indication would not necessarily change the 2018 version of the AACE algorithm because GLP-1 receptor agonists are

already top listed as a choice for antidiabetic therapy.

Finally, I want to emphasize that AACE does not advocate for approval for indication for any specific drug. However, since our mission is to provide our membership with the tools for the highest quality of care, expanding the list of new medications and indications will approve management of the ever-increasing burden of type 2 diabetes.

To be able to utilize effective and safe medications to improve metabolic control with less hypoglycemia and hopefully cardiovascular risk reduction can only benefit patients with type 2 diabetes. Thank you so much for your attention.

DR. WILSON: Thank you very much. Speaker number 10, please introduce yourself and any organization you represent.

DR. DARSOW: Good afternoon. My name is Dr. Tamara Darsow, and I'm senior vice president for research and programs at the American Diabetes Association. I have no financial conflicts.

The ADA represents 14,000 professional

scientists and clinicians, as well as the 30 million people living in diabetes in the United States. The ADA does not advocate for individual products. However, we strongly support the need for continued innovation and research toward new therapies that improve the management of diabetes and address the persistent, unmet needs that exist for people living with diabetes.

The ADA has been publishing standards of medical care since 1989, and these standards are updated annually to include new clinical research findings and new therapies, and they're internationally recognized as premiere evidence-based guidelines for diabetes.

The standards recommend patient-focused care, emphasizing the importance of choice, flexibility, and individualization to achieve the best outcomes. The standards have also long championed comprehensive management of diabetes, including in consideration of not just hyperglycemia, but the comorbid conditions that exists with diabetes.

One of the most urgent needs in diabetes is a reduction of cardiovascular risk. Diabetes is an independent risk factor for cardiovascular disease, as you've heard today. And despite significant advances in glycemic management and cardiovascular risk management over the last few decades, cardiovascular disease remains the major cause of morbidity and mortality for people with diabetes.

People with diabetes are 1.7 times more likely to die from a cardiovascular event than people without diabetes, and care for people with diabetes accounts for one in every $5 in healthcare spending in the United States. Cardiovascular disease is, of course, the major driver of these costs. Reducing cardiovascular risk in people with diabetes therefore remains a critical objective of comprehensive diabetes treatment.

Diabetes and cardiovascular risk factor management have traditionally been addressed individually, treating hyperglycemia, hypertension, and hyperlipidemia, with multiple medicines in combination. Even with or perhaps even because of

the complexity of this combined care, recent data suggests that few people with diabetes actually achieve combined treatment targets. Therapies that address hyperglycemia while reducing cardiovascular risk have significantly improved outcomes for people with diabetes.

Over the last decade, concerns regarding the cardiovascular safety of diabetes medications have led to regulatory requirement for these outcome studies, and while the majority of the new therapies that have been subjected to these rigorous studies have been shown to have no cardiovascular harm, very recently, several medications have actually demonstrated a benefit in patients who are at high risk for cardiovascular disease.

These medications were added on top of standard of care for cardiovascular risk factor reduction, and therefore appear to address at least part of the residual risk that exists even after optimized treatment with current agents.

Now we have the evidence that agents that

primarily treat hyperglycemia can also, in some cases, have a favorable effect on cardiovascular disease, and it's critical that this information is clearly communicated to the medical and patient communities.

The enormous burden of cardiovascular disease in people with diabetes requires that these medications be recommended to the patients that need them the most. This, again, gets back to the importance of keeping the differential clinical needs of people with diabetes in mind and matching therapeutics to their specific needs and clinical goals. Thank you.

DR. WILSON: All right. Thank you very much. Now speaker number 11, please introduce yourself and 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 representing dQ&A, a diabetes and obesity focused research company that provides pharmaceutical and medical device companies, as well as many leaders in the field, with insights

about patients from a panel of nearly 5,000 people with diabetes.

By way of disclosures, I'm an associate at Close Concerns, a San Francisco based healthcare information company, also focused exclusively on diabetes and obesity. My colleague, Payal Marathe, will review Close Concerns' disclosures later this afternoon.

I believe that an updated label for Victoza reflecting its cardioprotective benefits could offer much needed hope in an era of widespread frustration about diabetes care. Recent data from dQ&A powerfully illustrates just how prevalent this frustration is and how much opportunity exists for improvement.

Earlier this year, [inaudible - audio gap] of the diaTribe Foundation, dQ&A surveyed nearly 3500 people with diabetes to assess their perceptions of their diabetes therapies. The responses were strikingly negative. Among people with type 2 diabetes, less than a third of respondents, 29 percent, indicated their current

diabetes care regime was very successful.

In slicing the data, we saw that only 27 percent of people with type 2 diabetes found their current diabetes care very successful at limiting frustration or discouragement about diabetes; and even lower 23 percent indicated their current diabetes care regime as being very successful at fostering freedom from worry about their long-term health outlook.

Often from the moment of diagnosis, people with diabetes are bombarded with fearful messaging about the urgency of managing their diabetes to prevent the sequelae of complications like cardiovascular disease. However, these findings from dQ&A demonstrate that patients have little confidence in their current diabetes therapies to deliver on precisely this.

If Victoza's indication were updated to reflect its ability to reduce cardiovascular events in high-risk patients, we believe that would deliver a great deal of hope to those very patients, as well as increased education and

discussion about the inextricable link between diabetes and cardiovascular disease.

According to a key publication by Dr. John Buse's group, 67 percent of people with diabetes don't consider cardiovascular disease to be a serious complication of diabetes, though 91 percent of their physicians do. There's a clear information gap between patients and providers on this front.

I was fortunate to be present at the unveiling of the LEADER results to a crowd of thousands of physicians, scientists, and advocates at last year's ADA. This was a singular experience in my time at Close Concerns as the most overwhelming display of optimism that I've ever witnessed for the future of diabetes care.

I wish everyone living with diabetes could experience the hope that filled the conference hall the day the LEADER results were announced, and it would be a shame not to emphasize the confidence inspiring results of this landmark trial on Victoza's label.

What also inspires confidence is Victoza's host of other clinical benefits, including weight loss and reduced hypoglycemia, in addition to the cardioprotective effect. These added outcomes beyond A1c lowering efficacy bode very well for patient adherence with Victoza, an issue that has traditionally been a challenge for the nearly 40 diabetes drugs approved in the last decade.

It's also worth noting that a label update for Victoza will likely help expand access and reimbursement for the GLP-1 agonist class more generally, which remains out of reach for an unacceptable proportion of people living with diabetes.

As you make your decision on a new cardiovascular indication, I hope the advisory committee will consider the impact that knowledge of the LEADER findings could have in empowering people with diabetes, that they can live long and live well.

I sincerely hope that the committee will vote today in favor of letting patients know that

they have one more tool in the fight against diabetes and its complications. Thank you for your consideration.

DR. WILSON: Thank you very much. Now, speaker number 12, please introduce yourself and any organization you represent.

MS. GAO: Thank you. Good afternoon. My name is Helen Gao, and I'd like to thank the committee for giving me the opportunity to speak today. I will be starting medical school this fall, and I'm here today as a future physician who hopes to work in diabetes.

By way of disclosures, I have spent the last two years working for Close Concerns, a healthcare information company based in San Francisco and focused on diabetes and obesity. My colleague, Payal Marathe, will review Close Concerns' disclosures later this afternoon.

Today I'd like to discuss the proposed indication of cardiovascular benefit for Victoza and the value of such a label update for patients and healthcare providers. With Close Concerns, I'm

fortunate to travel to dozens of scientific meetings a year attending hundreds of presentations. Few sessions generate as much interest, excitement, and hope in the diabetes field as CVOT results.

Yet, after the LEADER results were presented at the ADA scientific sessions last year, I was surprised and disappointed to see that these results weren't front page news in the mainstream press. I wondered how the average patient or the average primary care physician, who has so many demands beyond diabetes, would learn of these impressive and meaningful results.

Indeed, a survey of diabetes educators conducted by San Francisco diabetes market research firm, dQ&A, 81 percent of respondents were not familiar with the LEADER trial, and only 3 percent of respondents stated that they were very familiar with the trial.

This was shocking to me. A 13 percent reduction in risk from major cardiovascular events and a 22 percent reduction in risk for

cardiovascular death is highly significant and clinically meaningful. And if diabetes educators are not aware of these results, who will be?

An updated indication clearly stating that Victoza can reduce cardiovascular events in high-risk patients would go a long way in publicizing this important information. Thanks to the FDA's 2008 CVOT policy, we are in an unprecedented era of generating clinical evidence about diabetes.

As healthcare professionals face increasing time pressures, it is difficult to stay current with the constant flow of new findings. Drug labels play an important role in educating healthcare providers, leaving them more time and energy to focus on patients. Furthermore, an updated label could have a substantial and valuable impact --

DR. WILSON: Could you speak a little bit more into the microphone? We have trouble hearing you.

MS. GAO: Oh, I'm sorry. Furthermore, an

updated label could have a substantial and valuable impact on clinical decision-making. In the same dQ&A survey of diabetes educators, after learning of the LEADER results, only 16 percent of respondents said that the results would have no impact on their clinical recommendations for patients at high risk for CV events.

How would this information affect the clinical recommendations of the other respondents? In this survey, 45 percent said that the LEADER results would make them more likely to recommend Victoza over other GLP-1 agonists for patients at high risk for CV events. In addition, 42 percent of respondents said they were more likely to recommend any GLP-1 agonist as a second-line therapy following Metformin for these patients, after learning of the results.

This is especially important considering that GLP-1 agonists are currently vastly underused in diabetes care, despite their demonstrated benefits on A1c, body weight, hypoglycemia, and now cardiovascular risk. In fact, a recent diabetes

care article by Dr. Kasia Lipska found that only 5 percent of U.S. diabetes patients were taking a GLP-1 agonist in 2013. For comparison, nearly a third of patients were taking a sulfonylurea, despite the unknown high risk of hypoglycemia with these frankly outdated agents.

As demonstrated by the dQ&A findings, a label update, and the associated increased awareness of LEADER findings could significantly improve adoption of these advanced agents. I sincerely hope the committee will vote today in favor of making it easier for healthcare providers to practice evidence-based medicine. Thank you.

DR. WILSON: Thank you. Speaker number 13, please introduce yourself and any organization you represent.

MS. MARATHE: Good afternoon. First, I want to thank you for this opportunity to speak on what I believe could be a very valuable and important label update for diabetes patients and healthcare providers.

My name is Payal Marathe, and I speak as a

representative of Close Concerns, a healthcare information company that aims to improve patient outcomes by making everyone smarter about diabetes and obesity. Inevitably, this also involves research and writing on cardiovascular health, and the discussion on heart-related diabetes complications is only growing.

The Close Concerns team, myself included, attends more than 50 scientific meetings each year, conversing often with a wide range of thought leaders in the diabetes field. As far as disclosures, almost 300 for- and non-profit organizations, including today's sponsor, subscribe to our fee-based newsletter called Closer Look.

I was in the room, or rather the large conference hall, absolutely overflowing with people last year when full LEADER results were presented at the ADA scientific sessions. There was an unmistakable excitement in that crowded hall, and the risk reduction for each study endpoint was met with resounding applause.

Since then, we've heard strong support time

and time again for the cardiovascular benefits associated with liraglutide. Subsequent analyses since the initial presentation of LEADER results have underscored liraglutide's robust cardiovascular benefit. Most recently, at ADA 2017 just last week, we learned that the cardiovascular data in LEADER consistently favors liraglutide over placebo, even when controlling for possible intermediate factors. These include concomitant medications from beta blockers to statins, concomitant insulin use, recurrent cardiovascular events, episodes of severe hypoglycemia, and more.

Previously, we learned at the European Association for the Study of Diabetes meeting, that there's no significant interaction between baseline heart failure and reduced risk for MACE events on liraglutide therapy, and we heard at EASD that there's plenty of evidence from animal models to show how a GLP-1 agonist might confer cardiovascular benefit independent of glucose lowering, possibly through anti-atherosclerotic effects.

In this context, experts have argued for the validity of LEADER results and what they imply about cardioprotection inherent to liraglutide molecule. But regardless of mechanism, thought leaders are bringing attention to how these landmark results should affect clinical practice.

A couple select quotes. From Dr. Hertzel Gerstein, "A stone falls today the same way it fell 200 years ago, but our theory of gravity has changed dramatically. You don't need to know exactly how a drug works to benefit from it, once you know what those benefits are."

From Dr. Juris Meier, "At a certain point, it's okay to be pragmatic. So even if we don't know exactly how we're saving lives, let's save lives."

This is the full weight of LEADER results. Liraglutide can extend and save lives among people with type 2 diabetes at high risk for cardiovascular events. As the latest CDC numbers show, cardiovascular disease remains the leading cause of death for people with diabetes. We're

clearly in need of cardioprotective diabetes therapies, and now that we have one in liraglutide, we need to get it safely into the hands of patients and providers.

The bottom line is that a 13 percent risk reduction for major cardiovascular events is huge for people living with type 2 diabetes, and it's huge for healthcare providers who want to be more successful in treating diabetes. The cardiovascular finding has been well-received in the diabetes field.

It is a missed opportunity, if not unacceptable, to keep this information tucked away when so many patients could benefit from liraglutide's cardiovascular effects displayed clearly on a product label. I look forward to the rest of the day's discussion, and thank you again for this time and opportunity.

Clarifying Questions to FDA (continued)

DR. WILSON: Thank you very much. We've now concluded the open public hearing portion of the meeting, and we will no longer take comments from

the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments that may have been raised in their most recent commentaries.

First, we're going to go back to the questions that we've had carried over from the FDA presentations. We have a list, and we'll go through for those who still want to ask those questions.

Dr. Wang, did you want to have a follow-up or no? We can come back.

Dr. Sanoff? Please remember to introduce your name into the record.

DR. SANOFF: Sure. Hanna Sanoff. I was wondering, in the U.S. subgroup analysis, were you able to look at the 3a versus 3b hazard ratios? Because I think that would help try and inform this discussion of high risk-benefit in the U.S. subgroup.

DR. CONDARCO: I did not perform additional subgroup analysis from that particular subgroup for

that particular endpoint. Sorry.

DR. GUETTIER: The applicant may have those data. You actually want the data that shows --

DR. SANOFF: Sort of the --

DR. GUETTIER: -- in the U.S. subgroup between the two inclusion criteria? Established versus high risk?

DR. SANOFF: Correct -- you've got it, yes.

DR. MOSES: With a word of caution, when we start looking at subgroups of subgroups, I think we get into some treacherous area here. But if we look at the U.S. population, you see a profile that is not unfamiliar from what you've already seen. Here you have at the top, the primary analysis, and then the MACE or primary analysis for the U.S. population at the 1.03 that you've seen.

For inclusion criteria 3a, you see a hazard ratio just to the left of 1, and then a somewhat higher hazard ratio for a very low number of events, with a 3-event difference between the two groups; as I said, very difficult to interpret this.

DR. WILSON: The next question is from Dr. Everett on the phone. Brendan? This is carryover questions from this morning for the FDA presentations. If you don't have it right now, we can come back to you, and you can let us know.

DR. EVERETT: Yes. Can you hear me?

DR. WILSON: Yes, we can. Speak up a little more though.

DR. EVERETT: This is for Dr. Hamilton. Specifically, I think we've talked a lot about the U.S. versus non-U.S. subgroup or stratified analysis. I guess my interest is a little bit -- some members of the committee have asked whether or not there might be differential medication use in the U.S. versus non-U.S. sites. And I think one potential way to get a sense of how these patients might or might not be different is to look at the placebo event rate in the United States versus the non-USA.

I think the numbers -- I think it's on -- it's not this slide actually, is it? I think it's a different one for Dr. -- sent it in an

email. Let me just see if I can find which slide it is. I'm sorry, but I think it's the slide that specifically looks at the breakdown of U.S. versus non-U.S. that was presented by Dr. Hamilton, which is not on this slide that you're showing now.

In any case, I calculated the proportion of patients with an event in the U.S. in the placebo group was 15.2 percent and was 14.7 percent outside of the U.S., which suggests that at least baseline treatment and I guess relative sickness or risk of those two patient populations are similar. That says to me that, broadly speaking, the patient populations included in the trial are similar in the U.S. and the non-U.S. And it doesn't necessarily explain why there's a lack of benefit of the medication in the U.S. subgroup except for, A, the possibility of just slicing and dicing subgroups too many times and arriving at a significant p-value, or I guess an alternative hypothesis would be the differential rate of study drug discontinuation that the sponsor has proposed as a possible --

DR. WILSON: Dr. Everett, we're trying pull up the slide you mentioned. Perhaps it's slide 16 in Kiya Hamilton's. Is that the correct one?

DR. YANOFF: We believe it may be slide 19 in Dr. Condarco's talk. We don't have the exact event rate, but we do reiterate that the rate of first MACE in placebo was similar between U.S. and non-U.S.

DR. EVERETT: Okay. That's really the essence of my question. Was the placebo rate similar in the two different populations, U.S. and non-U.S.?

DR. CONDARCO: That's correct. To quote Novo Nordisk's briefing document on page 46, the rate is 3.97 versus 3.89 events per 100 patient-years.

DR. EVERETT: Great. Okay. Thank you. And sorry for the long-winded question for a short answer.

DR. WILSON: Dr. Konstam?

DR. KONSTAM: I just want, for Dr. Condarco and maybe the rest of you guys, I don't remember

hearing much or anything in your presentation regarding the on-treatment analysis that the sponsor proposed, which is I guess their only viable hypothesis about what could represent the basis for the U.S. difference.

I just wonder if you could comment on that, because I think that obviously this is an issue that's concerning. What do you think? Is that a viable explanation for it or not?

DR. GUETTIER: I think Dr. Condarco said that we were not ready to -- in her talk -- to actually -- that we weren't really onboard with regards to what -- we're not able to explain the differential effect based on the exposure alone. It might be a long-winded answer, but just bear with me for a second.

The sponsor did on-treatment analyses, and if you're actually going to look at whether or not exposure affected the outcome, those are probably not the analyses that you would do. I think that the analyses that you would do are technically complex, and we did not do them internally.

We did ask the sponsor to adjust for exposure in the Cox proportional hazard model, and when they do that, it does not explain away the differential effect. It's also not probably the most accurate way to actually answer that question.

Again, I think this sort of delves into the world of statistics, which is sort of beyond what I can answer. But actually to take into account exposure, you need to do some post-randomization. You'd have to play around with post-randomization, and it becomes very technically complex. So we did not do these analyses, yet.

DR. KONSTAM: Can I defer to my colleague to comment?

DR. WILSON: Dr. Neaton, you had your hand raised. Perhaps some clarification if it's --

DR. NEATON: Well, it was before the break. This relates to it. I'm actually very suspect of the on-treatment analysis because an awful lot of events are left out of those analyses. I think you're not comparing like-with-like. Without a lot more detail, I think they're very hard to

interpret.

With that as background, what I thought was interesting analysis this morning was the analysis of U.S. versus non-U.S. for treatment differences in hemoglobin A1c. What I thought I heard the FDA say this afternoon is that they didn't see any differences, but from the graphs I recall seeing this morning, there was evidence of some differences I thought.

Maybe the sponsor can put them back up. Because those are intention-to-treat analyses, as I recall, showing hemoglobin A1 differences between treatment and control for the two subgroups.

DR. MOSES: Dr. Neaton, is this the slide you're referring to?

DR. NEATON: This is it, and I don't know whether you've done the tests for interaction here, but at least this slide suggests there's a greater loss of different treatment difference in the U.S. population.

DR. MOSES: Yes. In response to some of your earlier questions, Dr. Blaha's in particular,

we have some additional evidence for whenever it is appropriate to convey to you.

DR. NEATON: Well the other thing that I thought of, prompted a little bit by the details of Dr. Hamilton's presentation, there's a fairly sizeable early treatment effect. It's hard to quantify from the Kaplan-Meier curves, but my best guess is that early in the first 12 to 18 months, you have as much of a benefit as you do overall.

So have you looked at the U.S. population in an intent-to-treat analysis just for the first year, or the first 18 months?

DR. KONSTAM: Or do we have a Kaplan-Meier curve just for the U.S. population?

DR. MOSES: We do have a Kaplan-Meier curve for the U.S. population. We have not looked specifically at the early events in the U.S. population.

DR. NEATON: That would provide some stronger evidence that it's related to people stopping medication later.

DR. MOSES: This slide shows U.S. population

overall, on the left, and then the on-treatment analysis on the right.

DR. NEATON: The U.S. population overall I think is what we want.

DR. MOSES: You have suggested that early in the course there may be more separation. There appears to be. I leave the interpretation to you.

DR. NEATON: Yes, I mean it doesn't look to me anything like the non-U.S. population, if you were to put it up there, by just taking out the subtraction.

DR. MOSES: Excuse me?

DR. NEATON: If you were to look at the non-U.S. population, I think this curve would look very different, just based on what the overall results were that we saw earlier.

DR. MOSES: We'll see if we have that. I don't believe we have that slide to put up for you.

DR. NEATON: I mean one other thing, obviously this is a small subgroup.

DR. MOSES: Exactly.

DR. NEATON: Have you looked at the expanded

base outcome for the U.S. population?

DR. MOSES: Yes, we have. Here's the expanded MACE and the post hoc analysis for U.S. versus non-U.S. population. You can see that the hazard ratio is just to the left of 1.

DR. NEATON: This post hoc analysis, this is all intention-to-treat?

DR. MOSES: Yes.

DR. NEATON: Okay.

DR. MOSES: All analyses are intention-to-treat.

DR. NEATON: Okay. To me, I put more weight on these analyses. I wanted to come back to another question with the FDA. Can I take time to do that now?

DR. WILSON: Yes.

DR. NEATON: It's a follow-up from this morning. As I understood this morning, when I asked the question of how you're counting events, I think I understood that sites were closed sequentially, and the common closing date varies according to how you logistically did this at the

end of trial.

But there's a statement in the FDA dossier, which says something -- I'll read it. It says that "If a stroke or MI was linked to a CV death by EAC, but the CV death occurred after visit 16" -- which I think is the closing visit -- "the stroke or MI would be counted as a fatal event, and the CV death would be included in the analysis."

Now, I took this to say that you're counting cardiovascular deaths after the closing date for a site. Is that correct?

DR. MOSES: There were no events in LEADER where a cardiovascular death linked to an MI or stroke occurred after visit 16.

DR. NEATON: Okay. That's good. The reason for asking is that the more impressive findings from your intent-to-treat, obviously, is cardiovascular mortality. These are all being counted through the common closing date that's prespecified for each site, as you see --

DR. MOSES: That's correct.

DR. NEATON: Okay.

Clarifying Questions to Applicant (continued)

DR. WILSON: Okay. Thank you very much. We're now moving back toward the questions that are carryover from the Novo Nordisk presentation earlier this morning.

Dr. Cho, did you have any -- no comments at this point?

Dr. Fradkin, have your questions been addressed so far?

Dr. Konstam, any more? No?

On the phone, Dr. Allegra, you had a carryover question from this morning from Novo Nordisk. Do you have --

DR. ALLEGRA: Yes. Thank you. This is Carmen Allegra. I had just one question. Do we have data on all causes of death in just the U.S. population? I don't think I saw that. The question is does it mirror the primary endpoint in the U.S. population?

DR. MOSES: You're asking for all-cause death in the U.S. population?

DR. ALLEGRA: Correct.

DR. MOSES: Overall all-cause death.

DR. ALLEGRA: Yes.

DR. MOSES: Yes. Okay.

DR. ALLEGRA: No. No, just in the U.S. population.

DR. MOSES: All right. We do, and it is correct, it does mirror the overall result in the U.S. There are very few inconsistencies in the U.S. results in terms of the actual data or breakdown by various components.

DR. ALLEGRA: Thank you.

DR. WILSON: Another issue of carryover, Dr. Blaha, I believe you had a request from Novo Nordisk.

DR. BLAHA: Yes.

DR. WILSON: Could you repeat your query?

DR. BLAHA: Sure. Mike Blaha. Maybe we can revisit the other question. Of course, we're all trying to learn more information about this U.S. population. I had asked earlier to see the A1c results. We saw those.

I also asked to see -- I understand there

are power issues. I understand the microvascular outcomes were not the primary outcome here, but I'd like to learn more about the U.S. population, the potential impact on outcomes that might be related to the drug. If we could see the microvascular outcomes for just the U.S. population, and then maybe compare that to the overall population, we could understand what's happening in the U.S. population.

DR. MOSES: Certainly. Let me try to frame that, Dr. Blaha, in a slightly different way because the committee already is spending a good bit of time talking about the U.S. subpopulation and its effects.

If I could have US-21 please? We've looked at this in a number of different ways, and what this slide shows is the days of exposures in the lowest quartile by region. This is taking the lowest quartile for each of the four regions: Asia, Europe, North America, and rest of the world. And I think you can appreciate that there is a dramatic difference in the U.S. population in terms

of that quartile with low exposure.

Why is that important? It's important because when we look at the A1c -- and this was a little bit back to the data we shared with you this morning -- for this particular quartile of exposure, in the U.S., you can see that not only does the A1c rise, but it actually rises above placebo levels, strongly suggesting that this is an off-drug effect in regard to glycemic control.

But that is not the full answer to your question about the microvascular disease, and the team during the break has actually looked at urinary albumin to creatinine ratio over time as another surrogate, if you will, because this was also the events that occurred with the greatest frequency.

You can see on the left, U.S. population; on the right, non-U.S. population. Again, the same pattern, that over time in the U.S. population, that the effects seen in the overall population and in the non-U.S. population are largely lost over time. Again, consistent with an off-drug effect.

In our mind, although this may not completely explain the overall results, it does provide us with some further confidence that exposure is a very important element of that.

If I can, let me have please, slide US-37, because this gets back to another question that was asked by the committee. And that was to look at the MACE events in the U.S. versus the non-U.S. population. That's at the bottom of this slide. You can see here. At the top you see the U.S. versus non-U.S. for overall MACE, and then you see the on-treatment analysis. Again, a reflection of drug exposure, and you see that the U.S. population's hazard ratio is reduced to clearly less than 1, and the non-U.S. population has remained approximately the same.

Now, let's look back at the overall subgroup because the subgroup discussion is critically important. It's really quite beyond my experience, but we have with us Dr. Janet Wittes, who's a real expert in the realm of statistics on doing subgroups, and I'd like to bring her to the

microphone.

DR. WITTES: I'm Janet Wittes. I'm the statistician. As a lot of you who know me, I can see some friends over there, I'm very skeptical about subgroup analysis. If I look at these data and ask what's my best estimate of the hazard ratio for MACE in people in the U.S., rather than in this U.S. as a whole, to me it's pretty close to 0.87.

I trust more the results overall than I trust the results in a specific subgroup. Why is that? Well, we know, and you've heard around the table from both FDA and from some of you, that subgroup analyses are treacherous. They're unreliable. They're variable. But recently, Salim Yusuf and I wrote a paper in the New England Journal looking at geographic subgroups in particular, because there are lots of examples of studies that have one region, one country being aberrant.

We try to ask ourselves, when you see that, is it likely to be real or is it likely to be the effect of chance, and we looked at lots of

difficult drugs, lots of different diseases, and we came up with a series of ways of asking the question of how likely is this to be by chance?

You've heard a lot of analyses from Novo. There's a lot more analyses. And again, when I look at the whole gamut of analyses run, I end up with the conclusion that if I had to guess -- if I had to bet on what is the hazard ratio for individual people in the U.S., I would come up with 0.87 or a little bit higher.

DR. DE LEMOS: Dr. Wittes, can I ask a follow-up question while you're up there? Can we pull up the subgroup, the other subgroup that we're not paying as much attention to, the 3a, 3b?

DR. MOSES: Yes.

DR. DE LEMOS: Because personally I think the implications are -- it makes much more sense that there could be a difference with that subgroup.

What I'd like you to comment on is whether you believe that the same argument holds for that subgroup, number one? And number two, whether you

think we have enough information in the primary prevention subgroup, based on the sample size, to be confident that the treatment effect is similar in that subgroup.

DR. WITTES: Well, I haven't thought about this subgroup the same way I've thought about the -- but again, I look at it as a very small sample size, a very small numerator, which is what counts, and therefore, a wide confidence interval, a lot of uncertainty, and a group that had a high event rate. So it's not as if it's a low event rate. So my own view is I would, again, take the overall result.

DR. WILSON: Before you go away, Dr. Wittes, Dr. Fradkin?

DR. FRADKIN: Just on that slide that you were just speaking to that showed the subgroups, the Hispanics were not there. Does that play any role in explaining the U.S. finding?

DR. MOSES: It does not, Dr. Fradkin. They had the same protective effect as the other.

DR. WILSON: Any more follow-up questions

for -- yes, go ahead Ms. Hallare.

MS. HALLARE: Diana Hallare. I would like to ask the sponsor, what are the effects of liraglutide on patients with chronic kidney disease? For instance, what's the effect on the hypoglycemia or the effects with regards to the MACE outcomes and other endpoints?

DR. MOSES: A short answer to that is that liraglutide actually had beneficial effects in patients with chronic renal failure, both in regard to MACE and in regard to the other specific endpoints that were looked at, including severe hypoglycemia, relative to the general population.

It is true that the risk of both MACE and hypoglycemia increases with decreasing renal function, as to be expected, but liraglutide was protective in both cases.

MS. HALLARE: Thank you.

DR. WILSON: Any more follow-up questions?

(No response.)

Questions to the Committee and Discussion

DR. WILSON: Okay. I think we're going to

move on to questions and discussion items. We're going to put that up on the screen, and I'll read it out.

We have two discussion questions. These are not voting questions. They are for discussion, and we want opinions voiced. So I'm going to read it out for those who need some help at this time after lunch.

Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results, the LEADER trial, assessed several non-CV -- this is focusing on non-CV safety outcomes -- including number 1) medullary thyroid carcinoma, number 2) pancreatic neoplasm and pancreatitis. We're heard others, but this is the focus of the question, these three elements.

Please discuss whether the data represented today inform the potential for a causal relationship between liraglutide use and these non-CV safety outcomes, and please also discuss whether additional studies should be conducted to further evaluate these.

Commentary, questions, clarifications? Dr. Blaha, did you have a comment?

DR. BLAHA: I was going to probably plan on following up on other people's comments. I just want to emphasize, I guess, one aspect we haven't talked as much about. But I believe we see an all-cause mortality benefit in the study, which is important, of course, talking about potential -- the net benefit in the study. Patients tended to die less. That's important.

Now regard to this exact question, do I feel like I had enough information to link a potential causal relationship between the drug and, in particular, medullary thyroid carcinoma, for which I think there were just one or two events in the study, pancreatic neoplasm, and pancreatitis.

I guess I can see that the rationale, the scientific rationale, for this drug that works in this way, it could have a pancreatic effect. The effect was seemingly dwarfed by the potential cardiovascular effect. To me, I didn't find compelling evidence at all in humans of impact on

medullary thyroid carcinoma.

It seems to me it would make a lot of sense to continue to follow pancreatic outcomes in these patients, which I think was described; I'd have to get reminded. But I think there's a plan to continue to survey those outcomes. But I keep reminding myself that there was an all-cause mortality benefit in this study.

DR. WILSON: I want to remind the panel that this is really -- these three issues, we're going to get plenty of chance to discuss other things and to vote for other things later. So it's the thyroid carcinoma, pancreatic neoplasm, and pancreatitis; so if we could focus on those.

DR. FRADKIN: Judy Fradkin from NIDDK. I think that the study does provide important data for the medullary carcinoma because when you look at the magnitude of the effect on MACE and the number of MACE events that you see in this cohort, and then you see that there are practically no cases of medullary thyroid carcinoma, I think having a black box warning really puts a lot of

people off taking this drug.

I mean when people see that it can -- they're being told that it can cause cancer based on animal studies, and here now with this much bigger study, you just have to look at the number of CVD events versus the number of medullary carcinoma events, and you have to think about what kind of effect that language potentially has on use.

Also, in terms of this black box warning where you said that the effect of measuring calcitonin is uncertain, I think now with this data -- I mean, I would defer to Dr. Burman, but it seems to me that if you're going to have 3 percent of your placebo group with an elevated calcitonin leading to all sorts of follow-up then on those people who have elevated calcitonin, you might now say that there is evidence that following calcitonin is not, in fact, valuable.

DR. WILSON: We have a question on the phone, and I'm going to call that next, but I want the endocrinologists just to provide us some

guidance -- they know who they are -- concerning the calcitonin following. But let's first get to Dr. Allegra on the phone.

DR. ALLEGRA: Thank you. It's Carmen Allegra. I just wanted to comment about the malignancies. I agree with the last speaker that there's precious little evidence for medullary thyroid cancer risk in what's a substantial size trial, and I think that's hugely helpful.

Now the issue of pancreas cancer I know is also a concern. From my perspective, although there seems to be potentially a numeric difference between the placebo and the treated group, the numbers are incredibly small.

I think, based on the fact that there is, as we heard from the FDA, there is almost no preclinical support for the development of pancreatic neoplasms in animal models, coupled with the fact that most of the diagnosis of pancreas cancers in both groups was very, very quick after they were enrolled on a study with, by my calculation, a median time of less than a year and

a half, or maybe just about a year and a half.

We know from exposure to other chemotherapeutics, other cancer-causing agents, or agents that we clearly know cause cancer, most of those agents don't result in cancers for at least a decade after the exposures.

So those two facts coupled together make me pretty comfortable that this agent isn't causing cancer. And I don't even believe it's accelerating the appearance of pancreatic cancer because, again, the median time to diagnosis in both placebo and the drug-treated groups were nearly identical. So I think in my estimate I would put those two cancers to rest.

The last piece is that there were other cancers, like melanoma and cervical carcinoma, where there was also an imbalance that favored the placebo group, but it's probably just chance alone. The numbers were really too small to say much more about that, and I'll stop there.

DR. WILSON: Dr. Burman?

DR. BURMAN: Thank you. I admit to being an

endocrinologist. My feelings are that I am largely assuaged by the information presented, that there is not a definite link or even a highly suspected link between the drug and medullary thyroid cancer or C-cell hyperplasia.

I would note that there are probably GLP-1 receptors in the C-cells, but I'd also note that the data on the serum calcitonin levels is quite appropriate and didn't show any specific abnormalities. The data in animals, looking at the association with the RET oncogene, was negative, as were other relevant animal studies.

I would note that I would like to continue the registry as you've indicated, and continue the black box warning because it does take a long time for medullary cancer or C-cell hyperplasia to show up, we believe. And I'd also note that there is a study from Dr. Kluse [ph] at Ohio State that the incidence of medullary thyroid cancer in the population who died of other reasons is 0.14 percent, and I don't think we've seen that being manifest yet. So, so far, I'm quite happy

with the results.

DR. WILSON: As an endocrinologist myself, who does not see much medullary thyroid carcinoma, and there are very few who do, my question back to Dr. Burman is, is calcitonin a useful monitoring tool, and what is your opinion of the data presented so far for this? Perhaps the FDA itself might clue us in a little bit more on what's going on in the registry, but first, your opinion.

DR. BURMAN: Sure. Thank you. Calcitonin turns out to be a really excellent marker for C-cell hyperplasia and medullary thyroid cancer. There are few reported cases of aggressive medullary cancer that don't secrete calcitonin and secrete variants such as procalcitonin. But the vast majority of times, it's a very, very good marker, with the caveat that other medications and diseases can elevate calcitonin to some extent. Mainly, any agent or drug that elevates gastrin will elevate calcitonin.

I think the cutoff that you picked, or the FDA picked, was 20 picogram per mL, and that seems

a reasonable cutoff. I'm sure that's been discussed before.

DR. WILSON: Does the FDA have anything further to add about registry details?

DR. GUETTIER: I'm going to call on our DEPI [ph] colleagues.

DR. WILSON: One is, it wasn't clear to me exactly what is being done in the registry in terms other than follow-up questionnaires.

DR. BRIGHT: Yes. My name is Trish Bright, and I'm an epidemiologist. If we could have the epidemiology or DEPI backup slides 42.

They're doing two different types of things. One is just monitoring for the U.S. MTC cases, and they used the North American Association of Center Cancer Registries. It has a three-year data lag, and if you look on the left-hand side, you just have the total MTC cases from all the registries in the U.S.

Then they used 2001 to 2009 data as the baseline, and then compared that to the 2010 to 2013, which is after the introduction of

long-acting GLP-1 RAs in the U.S. market. On the right-hand side, you have the age adjusted incident rates, and you can see that there's an increasing trend during the baseline period.

If you go to the next slide, on the lower right-hand side, you have the expected estimates that you would have if the trend continued. Just to the left, those are the actual age-adjusted incident rates for 2010, '11, '12, and '13. So you can see that they're lower than expected.

Then if you could go to the next slide, there are limitations however. The cause of the baseline increasing trend is unknown, and it's unknown if the trend will continue.

The proportion of the MTC cases with prior exposure to long-acting GLP-1 RAs might be dwarfed by the cases associated with other risk factors or idiosyncratic cases, and the duration of any long-acting GLP-1 RA exposure and duration of follow-up are relatively short for the evaluation of the MTC and malignancy.

Go the next slide. This is the second half

of the registry. Participating state cancer registries, there were 28, they reviewed case reports to identify malignant MTC cases. They apply pre-defined criteria for malignant MTC. The registry obtains consent, which differs by state, and they do administer a questionnaire over the phone, which is required to capture the long-acting GLP-1 RA exposure.

Next slide. So on the top portion of this, as of the last reporting period, you have the total that were currently enrolled in the registry. The bottom portion are those that completed enrolment in the registry.

Then if we go to the next slide, the numbers that are highlighted here are those that have telephone data, so it's a total of 780 cases with telephone data. However, only four of these have reported possible long-acting GLP-1 RA use.

Next slide. Of the four cases, the first one is a patient-reported exposure to long-acting GLP-1 RA for 6.9 years prior to the MTC diagnosis, but had no history of diabetes. A physician

verification form was sought, but not obtained.

The second is a patient reported having a thyroid nodule prior to the MTC diagnosis, having a history of type 2 diabetes, and exposure to long-acting GLP-1 RAs for 1.5 years prior to the MTC diagnosis. The physician verification form was received from the endocrinologist, but the patient was not exposed to any long-acting GLP-1 RAs. There were attempts to contact a second treating physician, but they were not able to do so.

The third was a patient reporting a history of type 2 diabetes and exposure to long-acting GLP-1 RAs for six months prior to the MTC diagnosis. A physician verification form was sought, but not obtained.

The fourth is a patient-reported history of type 2 diabetes and exposure to long-acting GLP-1 RAs for approximately 8 months prior to the MTC diagnosis. A physician verification form was completed from the patient's endocrinologist that verified the diagnosis of the diabetes, as well as medications taken.

If we go to the next slide, this is just characterizing the capture rate. On the left-hand side is the total cases from the NAACCR in the U.S. On the right-hand side are the cases in the registry for the years 2010 through 2013, and there is the 3-year day lag.

You'll see in 2012 and 2013 that it's running about 20 percent. These are people with telephone data, so about 20 percent. The other two years, 2011 and 2010, it's somewhat lower, but that's because a lot of the state cancer registries didn't come on board right away, and they're catching cases retrospectively. We expect this will increase, but this does speak to the short period of follow-up, so we should keep that in mind.

If we go to the next slide, in conclusion, the 4K MTC cases with possible exposure to long-acting GLP-1 RAs do not suggest an MTC safety signal coming from the registry, but the duration of long-acting GLP-1 RA exposure and the duration of follow-up were relatively short to evaluate for

MTC.

Are there any other questions on the registry?

DR. WILSON: I think not. Thanks very much. I have a question related to the topic -- it would either be the FDA or perhaps the sponsor -- of the cases that were identified. And this was clarified in the last couple few slides in the FDA presentation, the LEADER results.

There are 8 cases -- I'm sorry. There were none. Those were papillary. So there were no cases. But the question is what happened for the people with the 3 percent in both arms with the high calcitonin levels. What sort of follow-up did they have that was different from others?

DR. MOSES: When the study was started, we actually created a calcitonin monitoring committee recognizing that calcitonin would be measured and found to be elevated in some subjects, just because, as Dr. Burman said, anything that elevates gastrin is likely to -- H2 blockers being a wonderful example -- increase calcitonin.

Those patients who had elevated calcitonin is referred to that committee. The committee deliberated on the clinical history and the level of calcitonin, and made recommendations in a blinded fashion to investigators in terms of appropriate treatment.

In the majority of cases, nothing was done other than follow-up unless there was evidence of thyroid nodules or persistent or increasing levels of calcitonin. Elevated calcitonins in this trial were actually most commonly found in patients with renal failure, which is another cause for increased calcitonin. So no specific plan of action unless clinically indicated.

DR. WILSON: Thank you.

Dr. Konstam, did you have -- no. I keep going back to 1, 2, 3. We haven't talked much about pancreatitis. What is the panel's opinion? Do we have enough safety data concerning pancreatitis in the use liraglutide? Dr. Wang?

DR. LOW WANG: Cecilia Low Wang. I was reassured by the data that was presented. First of

all, I guess I'll comment quickly on the medullary thyroid carcinoma in that there are no cases found during the LEADER trial, and I think that of course we should continue the collection of data in the registry, as I think that's super valuable, but I was very reassured by that.

In terms of pancreatitis, I also didn't see a difference between the two groups. I was a little concerned that we really don't have enough data regarding pancreatic cancer, so I think we need to continue collecting data for that. But my concerns about pancreatitis were laid to rest, at least so far.

DR. WILSON: Any further comments about this discussion point? So I'm going to attempt to summarize. Oh, before I -- I'm off the hook for a second here. Dr. Konstam?

DR. KONSTAM: Just a word of caution. Well, I'll say two things. One is, I think I'm seconding Michael's comments that the rates here pale compared to the cardiovascular event rates. Whatever level of concern we might have about these

things, unless we know the patient is particularly at risk for medullary carcinoma of the thyroid or something else, I don't know what you'd do with the information, because the event rates pale compared to that.

Conversely though, just a word of caution. The rates are extremely low, so you can't tell whether or not liraglutide is doubling, or tripling, or quadrupling the rate of medullary carcinoma of the thyroid. The ambient event rates are so low. So just a word of caution with regard to all of these event types.

DR. WILSON: Dr. Wang?

DR. LOW WANG: Sorry. Just one last thought. Cecilia Low Wang. One last thought is that I did notice that about 27 to 30 percent of patients in the LEADER trial were exposed for 3 years or less. So I think in terms of thinking about safety, pancreatic cancer, medullary thyroid carcinoma, pancreatitis, I don't think the trial was long enough for enough of the patients to really lay to rest this question of safety.

Even though the goal of the trial was to enroll patients and have them in the trial for at least I think it was 42 months, really, about 30 percent of patients did not reach that. They were in the trial for 3 years or less.

DR. WILSON: Okay. I'm going to summarize the discussion, and what I missed, you all get a chance to correct and amend.

The non-cardiovascular safety outcomes, the comment, especially made by our cardiovascular colleagues, is that the event rates are extremely low in comparison to the cardiovascular-related outcomes. We're talking about a very small percentage of people for any one of these three outcomes.

The first is the medullary thyroid carcinoma, which thyroid cancer is relatively common in the United States, but this is one of the rarest of the thyroid cancers. It's really uncommon. With the exposure information that's been accrued so far in this trial, and in other studies, and in ongoing registries, it may take a

while to really see a signal, and this has been emphasized by several of the panel.

Some of the concerns as the data are accrued, pay attention to person-years of exposure; potentially how long ago somebody might have taken a medication that caused a trigger even, if that's a possibility; a variety of epidemiologic issues how to track the incidence, and potentially the changing incidence of this rare cancer. That's number one for medullary carcinoma.

Endocrinologists, in general, feel that monitoring calcitonin is a prudent way to go for somebody who is at risk. For instance, this is used in patients who have familial predisposition to this. We don't know exactly how well that might work in this population group. I'm not sure. Outside of trials, there has been data accrued to know. It's an unanswered question in my mind, but that's something to consider; is this a possibility moving forward?

The second issue is pancreatic neoplasm. It was felt that this was uncommon, and there was

really not much difference between active therapy and liraglutide therapy for pancreatic cancer. And there's little animal data to support it, in contradistinction to some of the animal data that have supported the concern for medullary carcinoma of the thyroid.

Similarly for pancreatitis, very little data to really super support a difference, but there is data that was not on our discussion. There is more consistent data to support difference in gall bladder disease and problems or abnormalities, diseases related to the biliary system.

I think there was support for the ongoing registry and to continue this. It's been mentioned that the registry is 15 years in duration, and we've heard numbers such as at least 10 years. I'm not sure we have the expertise to agree or disagree with any duration, but there is concern that cancers of the thyroid take a while to develop and to be diagnosed.

That's my summary, but I'm open for amendments. Dr. Budnitz?

CAPT BUDNITZ: Yes. Dan Budnitz. Very excellent summary. I've just got one other comment about a non-cardiac adverse outcome and something that was talked about that's common. And that's hypoglycemia, and I think this data just adds reassuring hypoglycemia data as a strength of this product that is quite meaningful for medication safety in general, particularly older adults that are on this. Again, this is an adverse event that's common, rather than quite rare like these others.

DR. WILSON: Okay. That's our first discussion question. Now we're going to move on to the second discussion. I believe what we're going to do, we're going to do the second discussion, and then we'll have a break. And then we'll come back and do voting. We're now 2:45. But that's just the general tone at this point.

Yes, Dr. Sanoff?

DR. SANOFF: Thanks. Hanna Sanoff. Just one follow-up question that Dr. Fradkin had mentioned earlier with regard to the black box

warning for medullary thyroid carcinoma I think is relevant for this group to think about. I really think we all feel that the cardiac risk really outweighs here the medullary thyroid cancer.

I'm sure all of the practicing clinicians in the room will agree it's a very difficult conversation when the person comes in and goes, "Have you ever read this?" Right? "Why the heck would I take this medicine?"

So while I think we just simply do not have adequate human data for medullary thyroid cancer, because it shouldn't take way too long from the data we have from any of the existing treated patients to know if it's an issue, I would suggest that perhaps the animal data aren’t really all that relevant right now, based on what we have for the label.

DR. WILSON: Okay. Thank you very much.

We're going to move to question 2. Tentatively, we will discuss this, then we'll take a break and come back for voting questions. Thank you.

Question 2. Please comment on the design, conduct, results of LEADER, and whether LEADER did, A, adequately addresses the post-approval CV risk assessment as recommended in the 2008 guidance on diabetes -- I won't read that whole sentence -- and then B, provide substantial evidence establishing that liraglutide reduces the risk of major adverse cardiovascular events. And it specifies cardiovascular death, non-fatal MI, or non-fatal stroke in adults with type 2 diabetes mellitus, and high cardiovascular risk.

In this discussion, consider the patients who were in the study, the reliability, clinical meaningfulness, and the consistency of the results for MACE and the subgroups.

Yes. Debra McCall, go ahead.

MS. McCALL: Debra McCall. I think we should relabel today as "Fun with Subsets."

(Laughter.)

MS. McCALL: In that vein, I'm going to introduce another one. And please forgive me, all the statisticians. These numbers will not be

enough to be statistically relevant or sufficiently power anything, but there's an advantage to me having been a family caregiver as a young child, and also being an apprentice to a genealogist in the family. And I have very strong medical histories from multi-generations.

I was also added to this advisory committee on short notice because your previous patient representative was not able to make it. But I'm really glad I am because my family is here. There's no doubt. They were not part of the study, but they're here.

For instance, in one major line of my family, there are 9 siblings. This is my parent's generation. Seven of them had non-fatal MIs by the time they were 50. This is expected in family.

Now, keep in mind that my family, we only have three incidences of cancer in three generations. These are non-smokers, non-drinkers, but they like to eat. BMIs are closer to 40, high stroke risk, high diabetes. Pick almost any cardiovascular risk except arrhythmias, and it's

rampant. And I'm going to address a few of these non-U.S./U.S. numbers that some of you are concerned about based on a family's experience with this.

In my parent's generation, 7 of 9 had a non-fatal MI by the time they were 50. On average, by the time they died, they had 3 MIs. Yes, that's a number I can track. In my generation, I'm one of the youngest. We've had 18 of my generation that had a non-fatal MI by the time they were 50, out of 21.

In the next generation, we have 30, and they are over 35. We've only had 4 non-fatal MIs so far in that generation. When I did a quick poll of my family, 16 of them are taking Victoza. So for me, that's clinically significant.

In the U.S. -- and I see this in my own family -- I also moderate an online patient forum for another cardiovascular issue, and it has 6,000 international members. From my own family and from the U.S. members that I see on my patient forum, they want all of their drugs to be 100 percent

effective with absolutely no side effects.

Now, we all know that doesn't happen, and when it does, I tend to see my own family, and unfortunately Americans on my forum complaining a lot about side effects. And that's a real reason why they stop or cutback, and don't tell their clinicians.

It's a sad thing. I looked at some of the data particularly that the sponsor gave on EF-11 and US-21, and you see those very high we're sticking to this drug no matter rates in Asia, but I think also, too it's a very different personality that you have between different countries.

Yes, I'm totally jealous that the European, the non-U.S. ones, were just beautiful straight lines and the U.S. were kind of bouncy. But I think that leads to my second reason of why it's quite possible some of those U.S. numbers are not quite as consistent as you'd like to see.

Other than the side effects, the other biggest issue, particularly with Victoza, that is experienced over and over in my particularly family

that I've helped deal with, are insurance and formulary changes. You can choose an insurance in the fall, Victoza will be on the formulary, and then they drop it in March or April, or some other time after the year, and then there's a 30- to 45-day arm wrestling to get back on it.

In the time frame, they're either not taking it, they're taking a significantly reduced dose, and thus numbers kind of get a little bouncy, and maybe the endpoints are not quite as clean as all of you would like to say.

I know in my own family, with just those three generations, it's a huge difference. So for myself, I think when I read this data and I looked at it, there's a clear cardiovascular benefit here.

DR. WILSON: Okay. Our next comment is from Dr. Kewalramani on the phone. Reshma?

DR. KEWALRAMANI: Thank you. I just had two comments to make on discussion point number 2 about the design, conduct, and results of LEADER. Reflecting back to the EMPA-REG trial, which I think many of the panel members, including myself,

were on, there are some similarities. Large, well-designed study, here with very low missing data, time and event controlled with a steering committee, adjudication committee, DSMB, I'm impressed with the design, conduct, and re-execution of the study.

I wanted to point out something that may have gotten lost in today's discussion. Here, while the primary endpoint and analysis was around non-inferiority, the superiority was prespecified, and I think that that adds rigor to what we are looking at here in terms of the results.

We spent a good amount of time on the subgroup for reasons that are very understandable. However, I'd like to just bring us back to how fraught with challenge and difficulty subgroup analyses are and look at the numbers when we look at the U.S. population in comparison with the overall study and put that in context.

DR. WILSON: Okay. Next comment, Dr. Oakes on the phone?

DR. OAKES: Yes. Thank you. First of all,

I would like to make a comment that I'm very impressed by the fact that all the components of primary outcome move in lockstep, which is different from what I've seen in a lot of other studies.

I do want to come back to the subgroup issue because I don't quite agree with Dr. Wittes on this. For this reason, I think the subgroup, which is looking at the U.S. population, which is the target population, if you like, the population for which the sponsor is seeking approval, comparing that subgroup with everybody else who is not in that subgroup, who will not be directly affected by this approval, I think does give it a somewhat additional status as a subgroup analysis. Therefore, I think the FDA's interaction tests, which gave a marginally significant result, are something we ought to take somewhat seriously.

Having said that, I do not take the view, that I think we've expressed with some of the comments, that basically because of the U.S. population is the target, we should therefore kind

of ignore the data on 73 percent of the patients and just focus on the 27 percent in the U.S. I think if that was the decision, then that decision should have been made in the design stage of the study, rather than now at this point.

So I'm somewhat on the fence here, that I think this subgroup is a special interest. There is some evidence that it is responding somewhat differently. The suggestion has been made, but no convincing evidence to my mind has been given, which would completely explain the difference.

That being said, I think in the final analysis, the full study data carries greater weight than the subgroup data. I think the part of the labeling should certainly draw attention to the difference in the two populations. Thank you.

DR. WILSON: Okay. Thank you very much, Dr. Oakes. Dr. Yanovski?

DR. YANOVSKI: Sure. First of all, I really do want to commend the sponsor also on the design and conduct of the study. In particular, I found the completion rate very, very impressive, and the

very little missing data really provided reassurance.

Again, I want to get back to the subgroups. For the U.S. subgroup, I actually found the explanation of possible lower adherence something that was convincing to me, particularly the slide that was shown, showing the glycemic control with liraglutide and how that tended to fall off over time. And I think it's also consistent with some other studies of U.S. versus non-U.S. populations.

But I want to come to also the 3a versus 3b subgroup, the group with pre-existing heart disease versus the non-CVD group. And I realize this is a really small group, and they had a very low event rate, but it is also possible that there's a differential effect in people with and without pre-existing cardiovascular disease.

The label is going for both prevention of high-risk CVD, as well as secondary prevention in people who have already had a cardiovascular event. So I'm just wondering if the data are compelling enough that this was useful in primary prevention

of cardiovascular disease.

DR. WILSON: Dr. de Lemos?

DR. DE LEMOS: James de Lemos. I also think this was a well-designed, well-conducted, high-quality trial that provides important evidence. I would agree more emphatically with Dr. Yanovski about the burden here.

The trial was designed to show non-inferiority, so enrolled a high-risk patient population to generate large numbers of events, and does that conclusively. But then when you flip the paradigm and say we want to use this drug to lower cardiac events in lower-risk primary prevention, that was 18 percent of the study population here with a point estimate that suggested harm.

So it seems completely inappropriate to me to offer an indication, if there's an indication given, to a group that is tiny and didn't demonstrate even a shred of benefit. And there is plausibility for drugs that work differently in secondary and primary prevention.

So I think it's fairly clear-cut that if

there's indication, it really has to be limited to the people in whom it was studied, which is secondary prevention. It was such a small subgroup of primary prevention.

To me, the big issue is it's a clearly successful trial. It all comes down, to me, to whether it meets the burden of single trial with robust enough evidence. I think if this came to cardiorenal with a primary endpoint that was 0.011, everybody would probably congratulate the sponsor and ask them to come back with another well-conducted trial, with some disagreement because of the benefit with all-cause and CV mortality.

I do think it's fair to debate whether this is different because the drug's already on the market, and whether it's realistic to expect a p-value that low in two 10,000-person trials for what's essentially an add-on indication.

I'd Love to hear what the FDA and other people think, but that to me is, if the bar is the same as if you rolled this drug in, forget a

diabetes drug, and said we're bringing this drug to cardiorenal to lower cardiovascular events and we're going to do this with a single trial, I don't think it quite makes it, although it's a great trial. But why should the bar be the same there when the drug's already available and we know it's safe? And that's the question I have.

DR. WILSON: Okay. Next, Dr. Konstam.

DR. KONSTAM: Well, I really resonate with everything that you just said. I actually think it would do a little bit better in cardiorenal, but I guess we could debate that over a beer.

I will point out something. Nobody's really talked about the EMPA-REG trial today, and the parallels, and the analogies. I think there are a lot of analogies. That to me was a more difficult challenge. And the reason was that the primary endpoint was more marginal than this in terms of the p-value, if I remember. I believe it was 0.04 around there, and that troubled me a lot, because that was one trial.

I think what everybody gravitated toward in

that trial was there was a much stronger p-value for the cardiovascular mortality component of the primary composite. The primary composite was at 0.04. The cardiovascular mortality piece of it was a much stronger signal, and people gravitated toward it, and there was a whole discussion around that.

So I think now coming back to this trial, I see four questions for myself. One is, is one trial enough in this case? Two is what do you do about the cardiovascular mortality endpoint, given that that's a component of the primary? Then three and four are the two subgroup issues.

As far as the one trial, I think it's pretty strong as a single trial. I guess the two-sided p of 0.011, 1300 events, which is really pretty powerful to me; substantial consistency across the components of the composite, which I think is a really strong point for me; and consistent with the prior data at any rate.

So to me, I think it adds up to a strong argument that it's compelling, despite the fact

that it's one trial. So that's my starting point with it. I think the cardiovascular endpoint signal is even stronger with a hazard reduction of 22 percent, 400 endpoints. I think that's a powerful driver of the primary, and I think that's one that I would think goes in the labeling.

I really agree with your comments about the -- and I think yours, Susan, with regard to the population. And I don't agree with Janet on this one. I think in this case, I think it's a small subgroup that is going in the other direction and a very different group than the other. These are two very different populations.

I mean, we're struggling to ask what's different about the U.S. population, but in the established cardiovascular and renal disease versus the ones at risk, they're very different populations. And there is not a hint of a benefit in the small subgroup, and I don't think you get from here to there. I think that in the labeling, I would say it's patients with established cardiovascular and maybe renal diseases. I think

that's the population that drove this endpoint.

The U.S. business, I really struggle with a lot. I basically am with Dr. Wittes on this. I'm a primary endpoint, ITT, don't mess with subgroup kind of guy. So I don't feel -- I'm uncomfortable with the U.S. thing. I'm not sure whether the dropout rate or the off-treatment rate accounts for it or not. If it does, that poses a whole other set of questions. Well, why are those patients in the U.S. going off the drug, and what does that mean from an effectiveness perspective? We haven't even touched on that.

So I'm very uncomfortable with all of that. Nevertheless, I'm still left with saying, okay, but at the end of the day, it's a subgroup with otherwise very powerful results. And I'm willing to go with that as the finding of the study. I think that the FDA needs to grapple with that further and think a little bit more about other explanations and also what kind of labeling to put in.

I think there is precedent for, if I'm not

mistaken, for approving a drug, and yet in the labeling making folks aware that, oh, by the way, the U.S. patients were not clearly contributors to this. But I think maybe it goes in the labeling. But I don't it detracting from the overall finding, which I think is a strong finding.

DR. WILSON: Dr. Burman?

DR. BURMAN: Thank you. Ken Burman. I just wanted to officially note my comments on 2a, does the study adequately address the post-approval CV risk assessment as recommended in the 2008 guidelines, which I have right here, and I think it does. There are minimal differences, but overall, it supports what the original guideline intent was.

DR. WILSON: Okay. Dr. Cho?

DR. CHO: Hi. Leslie Cho. I want to reiterate what everyone said about 3b. I think one thing that surprised me when I read the indication that the sponsor was going for was how broad the indication was.

If you look at the EMPA-REG, which many of us sat on that committee, it was a very defined

indication, whereas this is a very broad indication for people with high cardiovascular risk. And I worry a little bit about how the clinician will take that. If you look at the 3b patient population, it was age greater than 60. I don't know what means in the outside world, if they will follow that to the intention of the trial. That's my one comment.

My second comment is, if I think of statin trial, for instance, where we clearly asked for a secondary prevention and a primary prevention trial to distinguish the benefit of the drug, that's what the FDA has always asked for. But to combine both primary and secondary prevention patients into one group and then to give that indication an approval, to me seems a little exuberant for the trial that we have before us.

It is an excellent trial. I think LEADER's design, conduct, and result is very reassuring and very encouraging for our patient population that have CAD, but to then turn around, broadly approve it for the rest of the population in the current

U.S., I'm a little bit troubled.

DR. WILSON: Dr. Rosenberg?

DR. ROSENBERG: Thank you. Yves Rosenberg. Comments on the results as a whole and the purpose of the design, I think we always complain of studies that are underpowered. Here, by design or not, we ended with a study that had twice as many events as was needed to answer the question. So it's not surprising that if there is an effect, one was observed, at least from a statistical point of view.

The problem is that the clinician is left with interpretation of what it means. Also, we have an 18, 20, 22 percent relative risk reduction. The upper limit of the 95 confidence interval is compatible with a less than 3 percent reduction.

I'm not contesting. I believe there is an effect. How clinically significant that is, that's a question that's to be left for interpretation, but I don't think that's really an issue for the labelling. That's an issue for guidelines and clinicians making day-to-day decisions with their

patients. When they consider everything, they also have alternatives of treatment, side effects, et cetera.

This effectiveness issue, of course that's related and brings us to the subgroup of whether or not it's related to the fact that patients drop off treatment.

Again, that's not an issue for the FDA. I believe the drug works. Whether it works in real lives, that's not the question really the trial is asking, but it is a concern. If patients in a well-designed, well-controlled trial like LEADER are dropping off like that, if it's a reason for decrease or lack of effect in the U.S., well, I think we all need to be aware of that and think of the consequences.

I'm not going to labor too much on the U.S./non-U.S. subgroup. I agree with the limitation of this interpretation, but I think that's still something that needs to be considered in the labeling.

Finally, in terms of subgroup of primary

versus secondary, I think it's a convenient way to delineate who should or should not receive the treatment based on level of risk. I'm not sure, especially in the diabetes population, that these populations are too different. The way I see it is that you need to look at the level of risk for each patient and whether or not it's high enough to justify the drug, if the patient may benefit, and the benefit-risk may be better based on the individual risk.

Now for labeling convenience, I understand that what can be done, and I understand also the -- but I notice that what's important is the level of risk. When you look at all the subgroups, those who have high level of risk will benefit more even if the relative risk is similar. I think I'll stop there. Thank you.

DR. WILSON: Dr. Hamilton, did you want to make a comment on this, or one of your colleagues? FDA's coming to the podium. Please announce yourself.

DR. WANG: Yun Wang, acting stat team leader

at Office of Biostatistics, FDA. Because we have discussed so much on the subgroup analysis, I think it's necessary for us to elaborate a little bit what FDA is thinking behind this subgroup analysis.

We need to be cautious when we talk about subgroup analysis because when we see the forest plot, the statistician's may look different from the clinician's because subgroup analysis, if you look at U.S. versus non-U.S., you look at the point estimate or the confidence interval, and say, oh that p-value is less than 0.05 or that p-value is greater than 0.05. That's not the correct way.

Actually, when we look at subgroup analysis, we should look at the interaction test first. What does interaction test mean? We say for U.S. versus non-U.S., we are not looking at, say, U.S. is nothing and non-U.S. is significant. We look at the point estimate for U.S. population versus point estimate for non-U.S. population, whether they are different.

After taking into account the variability in those point estimates, we have the interaction

tests, and we come up with a p-value of 0.048. That's above 0.05. What does that p-value mean? That p-value means marginally that the quantity in the estimate for the U.S. population and the non-U.S. population may be marginally different, but that difference is not qualitative.

Why I say that is because you see that U.S. population point estimate is about 1.03, and you cannot say that's detrimental because the confidence interval still covers 1. And for the non-U.S. population, the point estimate is about 0.81, and the confidence interval for U.S. population and non-U.S. population overlap.

So we have to be cautious when we interpret the subgroup analysis. We disagree with the sponsor's on-treatment analysis, and I also personally disagree with what Dr. Janet Wittes says that the point estimate for U.S. population may be around 0.87. I don't think -- based on the data we have right now, we do see some quantitative difference between U.S. and non-U.S. population. Thank you.

DR. WILSON: Thank you very much. Next, Dr. Robbins?

DR. ROBBINS: I'm not going to belabor the subgroup analysis, except to say that I'm troubled by it. It's going to cause me some despair when I have to make up my mind about it.

I want to get back to what I said earlier. This was largely a trial of 1.8 milligrams per day. And partly, when I have my clinical hat on, I probably would agree with Alan Moses that maybe half of my patients are up to that dose. And I would argue that this is not a trial of Victoza in general. It's a trial of Victoza at 1.8 milligrams showing these effects.

This would be the equivalent of taking perhaps rosuvastatin at 80 milligrams and saying that it's effective across the board, and then someone prescribing 20 milligrams and making that conclusion. I don't know if I'm getting too picky on this, but I tend to see these studies as weighted as much possible to favor the product, rather than the real world, and that bothers me.

DR. WILSON: Dr. Budnitz?

CAPT BUDNITZ: Dan Budnitz. I'm going to belabor the subgroup analysis a little bit because voting is going to give me indigestion. Comments are going to mirror some of Dr. Cho's points, but will expand a little bit.

I do think this is a very well-designed study. The robustness of bio status was great. The worst-case tipping point analysis was very convincing. Expanded MACE results are convincing overall. I do think the intention-to-treat analysis provides support that it's effective, and the number needed to treat of 98 all-cause mortality for 3 years is clinically relevant.

But that being said, I think we would come to the question of do we have enough evidence for a single-trial indication. And I'm not talking about safety anymore; I think that's convincing, but for indication for cardiovascular benefit.

I thought I understood that FDA follows basically three considerations to approve a new indication for a drug with a single study. One is

that it could be similar to a pharmacologically similar drug, similar results to a pharmacologically similar drug. We don't have that here. It's kind of first in class. Another one is biomarker supporting data. And again, we don't really know what the mechanism is. We don't have biomarker supporting data.

Then I think the third point, as I understood it, is very statistically convincing evidence. Here's I think what we've been talking about with the subgroup. I'm talking about the U.S. versus the rest of the world, and this is a prespecified analysis for interaction. And we have an interaction term that's less than 0.05 that's prespecified. Well, if we're not going to pay attention to it, why are we doing this? Why do we look at it?

Again, I don't come from the clinical trialist world, but from an epi world of cohort and case control studies. And once you have that, I mean, you're done. You can analyze the group separately.

I think it's problematic and it's different from the EMPA-REG trial because there we didn't have a significant p-value for interaction, so I think that is a fundamental difference between this trial and the EMPA-REG that we'll have to consider later on.

DR. WILSON: Thank you. Next is Dr. Brendan Everett on the phone.

DR. EVERETT: Hi. Can you hear me, Dr. Wilson?

DR. WILSON: Yes, we can. Go ahead.

DR. EVERETT: Okay. I don't want to belabor the point but do want to reiterate I think some points that both Drs. Konstam and de Lemos made. And that is, my perspective as a part-time clinical trialist is that when you run a trial that includes a secondary prevention and a primary prevention population in the trial, it is, de facto, a secondary prevention trial because the patients who have the events are the ones at highest risk, and they're, of course, the secondary prevention patients.

That's just to reiterate something that people have said multiple times, which is that not only were most of the patients in this trial secondary prevention, or 3a I guess as we're calling them, but actually 88 percent of the events were in that category as well, with only 12 percent in the so-called lower risk or primary prevention cohort.

I think with that caveat or with that understanding, I think the trial was very well-designed, conducted, and the rigorous follow-up I think is an important point to emphasize. The overall number of events, and particularly the consistency of effect, which is something that we did not see in the EMPA-REG meeting approximately a year ago, is important, and I think it is satisfying or at least less likely to give at least myself indigestion when thinking about this.

I think Dr. de Lemos' comments about the product already being on the market makes the question about how rigorous to be and what level of

evidence to require for a label. It does I think affect that judgement a little bit.

Lastly, I think there is an effect on overall mortality here, but as we have seen in other trials in similar populations, that is of course driven by the effect on cardiovascular mortality. And in that case, we had nearly 500 cardiovascular deaths in this trial, which is a substantial number, and I think as many as you can expect in large trial to begin to make some inferences about the effect on important, very important, endpoints for patients. And with that, I'll stop there.

DR. WILSON: Thank you. Dr. Blaha?

DR. BLAHA: Thank you. Mike Blaha. I agree with so many of the comments, including Brendan's that we just heard. To address 2a real quickly, I think it's a very well-done trial for all the same reasons people have mentioned.

I want to get back to, a little bit, this 3a/3b question real quick. I hear what my colleagues are saying on this, but if I'm reading

this correctly, I don't think the 3a and 3b map onto our traditional cardiovascular primary and secondary prevention -- as well as we would like to think on first glance -- people were heard using the terms "primary" and "secondary" prevention.

When I look here, you can be in 3a if you have a 50 percent stenosis on an angiogram without symptoms, I think, which many of our primary prevention patients would be there. If you have chronic kidney disease, you get into 3a. If you have class 2 heart failure, you get into 3a. So it's a little bit different than our traditional you've had a myocardial infarction.

Let's say you've had a stroke. You could have a stenosis. You could have chronic kidney disease. You could have heart failure. But in 3b, you could have an ankle brachial index less than 0.9, which is suggestive that you have a lower extremity disease. You could have left ventricular systolic dysfunction.

So I have a little hard time putting these into a distinct primary and secondary prevention

basket and our traditional cardiovascular hat on. While I agree in general -- we think about primary and secondary prevention somewhat differently, although I think there is a continuum there -- in my case, my reading is I have a harder time saying, for example, this works in secondary and doesn't work in primary prevention, for example.

There's a clear continuum here from class 2 heart failure in one group to systolic dysfunction in one group; greater than 50 percent stenosis in one group; ankle brachial index low in the other group; and chronic kidney disease, which we've done primary prevention trials in chronic kidney disease. It's a little murky here.

My perspective was less to make a big deal of that distinction, but I didn't have as much problem with the wording of "in high-risk patients" because, frankly, in clinical practice, I'd be likely to think about a drug like this in high-risk patients.

Those are my comments about primary and secondary prevention.

DR. WILSON: Dr. Fradkin?

DR. FRADKIN: Judy Fradkin. I agree with most of the comments of my fellow panelists, particularly how well done the study was and how complete the follow-up was.

When I think back to the EMPA-REG trial and compare this to EMPA-REG, the two things that really stand out for me are the consistency of the findings. Even though only the CVD death as a subcomponent of the MACE was statistically significant, we did see both the non-fatal MI and the non-fatal stroke showing a trend in the same direction, which I feel is important.

I was also impressed with the curve, where we really saw a very steady splaying out of the effect, which seemed to be growing over time, which gave me also confidence. And those two findings made me think that this might really be more likely to be affecting the progression of atherosclerosis rather than the fatality of an acute event.

That said, I think the population studied was predominantly a population with established

CVD. Even though I think it may well have implications for people without established CVD, I think by and large, the findings were in people with established CVD.

With regard to the subgroup, I think the U.S. subgroup was a very small -- I mean, it was only 25 percent of the population. I think the confidence interval there included the overall finding, so I would not feel comfortable concluding that the U.S. population was different from the overall.

I'm a firm believer in intention-to-treat and looking at the entire study population. I've certainly been burned before with subgroup analyses, which then don't repeat when you go back to try to confirm a subgroup analysis.

Then the final thing I wanted to say was nobody's talked about semaglutide, but the fact is that there are two positive studies for CVD with this class of drugs. So to the extent that that's a criterion for being able to use one study for a particular drug, I would just point that out.

DR. WILSON: Okay. Dr. de Lemos?

DR. DE LEMOS: I was going just say, I don't disagree with Marv's point. The difference in EMPA-REG is that they did not in come in for the composite outcome; they came in for CV death, and the p-value there was an order of magnitude lower, as a single trial. But I think the point the buttressing evidence from the CVD death and totally mortality here really gives me confidence -- what I would consider to be a borderline p-value for a single trial really gives me confidence.

Just to Dr. Blaha's point, I do think that the burden is on the sponsor to prove, right -- because the world of people that might get this for CVD reduction is much larger in the group 3b than 3a. I think the burden is on the sponsor to prove to us that it lowers cardiovascular risk in that population to get the indication.

It may well do it, but with 12 percent of this population and no benefit, I just think it's their obligation to show that, and the trial that

they enrolled didn't do that.

DR. WILSON: Dr. Wang?

DR. LOW WANG: Cecilia Low Wang. I agree with many of the comments that have been made, and I just wanted to commend the sponsor and the steering committee on a very well-designed trial, investigators on a very well-conducted trial. It's a very, very low withdrawal rate, very low loss to follow-up.

Then just thinking about this U.S. versus non-U.S. population and whether or not this shows cardiovascular safety, I'm reassured by the fact that the upper limit of the 95 percent confidence interval for the primary endpoint is 1.25. Even then, I think it's safe even in the U.S. population.

Again, going back to the subgroup of the subjects enrolled in inclusion criteria 3a versus 3b; 3a, granted it isn't only established atherosclerotic cardiovascular disease; it's also stage 3 or greater CKD. I think that's really the main addition to 3a.

I'm very concerned about approving this indication for all patients at high risk for cardiovascular disease because if you look at the patients enrolled on 3b, so no established ASCVD, that point estimate, as has already been mentioned, is 1.2 overall, and then 1.4 in the U.S.

So I'm concerned about that indication. But otherwise, I think in terms of cardiovascular safety, I think this trial clearly showed that. The question is that added indication, I think it's a little too expansive the way it's worded.

DR. WILSON: Dr. Neaton, any further comment?

DR. NEATON: Just a few things to add to what's already been said. When I looked at this report for the first time, my eyes immediately caught CVD mortality and all-cause mortality. I find the results there very striking, and the all-cause basically is being driven by CVD.

The fact, that's already been stated, is that the other components are supportive, and the fact that with regard to death, they almost had no

missing data at all. So one can be very, very confident, I think, in the CVD mortality and all-cause findings, in the sufficient evidence, substantial in my mind, in terms of the indication for prevention.

While I understand the FDA's point of view in looking at U.S. versus non-U.S., that was not the prespecified subgroup. The prespecified subgroup, as I understand it, was four groups of people: Asia, U.S., Canada, Europe, and the rest of the world.

Actually, if I were doing this trial, an international trial, that's the way I would have prespecified it too. I wouldn't have just defined a 27 percent subgroup versus the rest of the world. You'd want to look at heterogeneity overall. There there's nowhere close for the interaction p-value being significant.

I think the exercise they went through to try to understand whether it was poor compliance was useful, but I didn't find it very convincing. It shows up in hemoglobin A1c, but it's not obvious

to me that it's translating to MACE. There may be something there, but it also could just be a fluke.

There were guidelines written a few years ago for the New England Journal of Medicine, which they probably had to adhere to when they submitted their paper, where you have to write down how many subgroups you looked at, in cautionary statements about even significant interactions that you find because of the number subgroups you look at.

After thinking about this for a while, I don't know what's going on there, but I don't count that as a very strong factor in lowering the substantial evidence that I see here.

DR. WILSON: Any more comments or are you all talked out? I think we're ready to summarize, yes? No? Yes, Dr. Cho, go ahead.

DR. CHO: I have a question for the FDA. When you give a label indication, can you put on the label type 2 diabetics with inclusion criteria and just list them, instead of the broad high cardiovascular risk? Have you?

DR. GUETTIER: I mean we could grant any

indication that we want, but usually we don't grant an indication based on the inclusion criteria for a study. Ultimately, the label is for prescribers and needs to be understood by the prescriber. And we, along with the sponsors, have to translate what the evidence actually shows for the patient population that will be treated. So we don't really repeat the inclusion/exclusion criteria, or else our labels would be just lengthy, i.e., lists.

DR. CHO: In my mind -- I just want to make it clear -- when you give a label approval, it is to guide the prescribers in whom there is a benefit for this drug, correct?

DR. GUETTIER: Right. You've spent all day trying to interpret what the results mean. We do that internally as well. Based on the evidence we have, we have to decide where the benefit lies, if the benefit's there.

DR. WILSON: Dr. Blaha, you had a comment?

DR. BLAHA: Yes. I just had another quick question. Maybe one of you all can help me answer it or the sponsor. I can't clarify it immediately.

Did we see exactly what fraction of people in the 3a group had CKD only or heart failure only? Are there entry criteria that didn't have an established ASCVD?

DR. MOSES: Are you looking for the percentage of the population or the MACE event in that percentage of population? Because we can actually do that.

DR. BLAHA: No, I'm looking for the former. I'm looking for just a baseline. There are lots of indications for getting into 3a group, two of which, heart failure for example and kidney disease, aren't ASCVD. So I'm looking for what fraction of the people got into the study based on those two.

DR. MOSES: In 3b?

DR. BLAHA: 3a.

DR. MOSES: 3a. Okay. Excuse me. Just one moment.

DR. BLAHA: How many people have CKD and how many people have heart failure, versus stroke or myocardial infarction.

DR. MOSES: All right.

DR. CONDARCO: You want to get an idea of how many patients had chronic kidney failure, so that would be --

DR. BLAHA: I guess there's going to be an overlap here. Some people have had a myocardial infarction and CKD. I'm looking for how many people got into the study based on CKD and heart failure but did not have existing ASCVD.

DR. MOSES: CKD alone.

DR. CONDARCO: CKD alone.

DR. MOSES: We have some of those data for you. If we can switch the projector over. Thank you. This is the breakdown for CV inclusion criteria 3a, and that is the, quote, "higher risk group." And you can see that was 81 and 82 percent respectively, and this is the breakdown. If you look at chronic --

DR. KONSTAM: That's not it. Because I think what that's saying is that 25 percent of the population had chronic kidney disease. I don't think it's telling us what percentage of the

patients had chronic kidney disease alone as getting in. I think that's what Michael's trying to get at; trying to understand whether really this is principally an established cardiovascular disease population or how much of it is just a chronic kidney disease population.

DR. MOSES: What we do have -- and again, I'm not sure it's getting right to your question, and I'm not sure we'll be able to get that given the time we have left in the day -- is the analysis of this population by looking at patients who have CKD only. You get the number of events there and the hazard ratio of 0.89, but it's not the actual total percent of the population. That we do not have, we haven't extracted at this point.

But it demonstrates that those with CKD only clearly also fall to the left with their hazard ratio, with broad confidence intervals.

DR. KONSTAM: But it's 108 out of the 1300 events?

DR. MOSES: That's right. As I said, it's a relatively small group.

DR. WILSON: Dr. Blaha, any further comment on that?

DR. BLAHA: No, I think that largely answered the question.

DR. WILSON: Any further comments, questions?

(No response.)

DR. WILSON: I have pages of notes here to try to summarize. This is a summary of question 2. If we could have it back up?

Dr. Burman was quick to clarify that he felt it very adequately addressed point 2a, and it was responding to the 2008 FDA guidance, and I believe all of us agree with him.

The controversies and discussions mostly we're facing were 2b, and the three different components, and the subgroups. It was said in about three or four different ways. One was consistency.

I favor Dr. Oakes. I've learned new words always from people with British accents. Lockstep is the one that stuck in my brain, beautifully

said, with a similar signal in the major trial result for cardiovascular death, non-fatal MI and non-fatal stroke.

The big concern was, number one, in the subgroups, one major subgroup, not a prespecified subgroup except by four major geographic group designs, was a U.S. signal that was not exactly in lockstep with the other three groups. And that was only 22 percent of the overall participants in the study and did not show a favorable effect, but showed a neutral effect and no harm, as was very well said different ways by different panel members.

The second one I think is more problematic is how to define it, is primary prevention, secondary prevention, and high-risk prevention. We've gotten used more and more with some of the trials using high risk. In diabetic patients, once they get past 45 or 50, they're all pretty high risk, so how do we even define primary versus secondary?

But as was very well-detailed by our

cardiovascular colleagues, this product appears to have especially worked for people who are getting clinical cardiovascular disease via an atherosclerotic mechanism. Those are the people who are benefiting. It doesn't appear to be some of these other groups, those with kidney disease; those with a left ventricular hypertrophy; those without evidence of being at high risk for atherosclerotic disease. There are some elements that, well, maybe they benefit, but it's especially those with atherosclerotic disease.

So I have trouble with those three terms, with the primary and secondary and high risk, and the idea that the two major groups are 3a and 3b, but the 3b group isn't exactly any one of those groups from the outset. So part of it is definitions.

A couple other comments that came up; one was the superiority was prespecified. That was a major point of discussion during the empagliflozin trial review, and that was also an issue there. These large trials often have a prespecified -- so

many of us feel that is a specially positive finding.

Let me see some of my other comments here. I think the letter and numbers that kept coming up was I'm not so sure what to say about the 3b group. What do I tell my patients if they fitted in to this group? Those were the clinicians, the cardiovascular clinicians and the endocrinologists who have patients walking in. If they had those types of diagnoses without a high risk or evidence of clinical cardiovascular disease, do I really generalize those results to my patient to prescribe this medication?

Dr. Budnitz also mentioned we lack mechanisms and biomarkers to understand what worked or how it worked. This came up with the empagliflozin, and it was of concern to all of the panel members, and it was a major issue of discussion. But there was less consistency. People kept saying over and over in our discussion, but this is fairly consistent across all the atherosclerotic cardiovascular endpoints.

I'm close to the end here. Everybody wrestled with should we recommend an approval, what will go on the label? I've learned to speak my heart at these meetings. That's the FDA's job is what goes on the label. What we say, especially when we come to votes that will come after our break, is we say what we think and don't think too much about the label. They'll figure out the label. I think that's the end of what I had to say.

Can we take a break now? Is that fine? We'll take a break, and we'll come back in 15 minutes at 4:00.

(Whereupon, at 3:45 p.m., a recess was taken.)

DR. WILSON: We have two questions. I'm sorry, it's item 3. Question 3 is the first vote, and then item 4 is the second vote. It's not like we've missed two votes. We're going to be using electronic voting, and let me explain that a little bit.

What we're going to do is I'm going to read

the question, then we're going to vote. Then we will go around the U of the panel members who are voting to explain why they voted, the rationale behind their vote. As I preface this, FDA leadership always tell us if it was easy we wouldn't be here. We are here to provide advice.

If you can't figure out which way to vote, yes or no, that's especially important to provide your rationale for the yes part and the no part because we understand you only get one vote.

For the voting system, the buttons will flash. Mine are already flashing, so if you're in the room you should have a yes, no, and an abstain flashing. We will all vote simultaneously, and then it'll be locked out, and your vote will appear on the screen.

We have some people voting who are on the phone. For those who are linked up, are we all set with them how that's going to go? All right, so they're all set.

I'm going to read the first question. Do the results of the LEADER trial establish that use

of liraglutide in patients with type 2 diabetes mellitus is not associated with unacceptably high cardiovascular risk? So it's yes, no, or abstain, and we're starting now.

DR. SANOFF: Is it supposed to continue flashing?

DR. WILSON: Mine's continuing the flashing, and I've already voted, so I believe so.

(Pause.)

We're waiting for those on the phone, because that has to be communicated. Those of you who are on the phone, I trust you're voting, Dr. Everett, Dr. Oakes, Dr. Allegra.

(Pause.)

DR. WILSON: We've been asked to re-vote here in the room. they're okay on the phone? So just here in the room, okay.

(Vote taken.)

CDR BONNER: For the record, 19 yes, zero no, zero abstain.

DR. WILSON: Dr. Robbins, if you would lead us off. We're going to go around the room starting

with you. So those of you who come after him, you will follow and think what you're going to say, starting off with you Dr. Robbins.

DR. ROBBINS: This one was easy despite a double-negative statement that we had to cryptically figure out. This is a very well-designed study, and I very much appreciate the obstacles and things that happen in clinical research. But I think for this question, it's very clinically helpful and convincing that this drug is certainly doing no harm.

DR. WILSON: Before we go forward, I've been reminded to please state your name and how you voted. So Dr. Robbins, just say it clearly for all of us.

DR. ROBBINS: That was David Robbins.

DR. WILSON: And you voted?

DR. ROBBINS: Yes.

DR. WILSON: Okay.

DR. SANOFF: Hannah Sanoff. I also voted yes. I don't have much to add to that. It was well-designed for this specific question and pretty

unequivocal results in my mind.

MS. McCALL: Debra McCall. Yes, for all the reasons already stated.

DR. YANOVSKI: Susan Yanovski, yes. I really have nothing to add. I thought it was pretty unequivocal.

DR. BLAHA: Michael Blaha. I voted yes. I think, without question, there is not an unacceptably high cardiovascular risk with this drug.

DR. BURMAN: Ken Burman, yes. I agree there's not an unacceptably high risk, and it was proven by this trial.

DR. CHO: Leslie Cho, yes. Ditto.

MS. HALLARE: Diana Hallare. I voted yes because it lowered the risk factors such as cholesterol and blood pressure levels and lowered MACE endpoint as well.

DR. LOW WANG: Cecilia Low Wang. I voted yes, and I agree with the others that the LEADER study clearly showed that this is not associated with unacceptably high risk.

CAPT BUDNITZ: Dan Budnitz. I voted yes. No additional comments.

DR. FRADKIN: Judy Fradkin. I voted yes also, clearly established safety.

DR. WILSON: Peter Wilson. I voted yes. And as was noted by some of the commentators in the earlier discussion, even the subgroups showed no unacceptably high risk.

DR. DE LEMOS: James de Lemos. I voted yes, nothing to add.

DR. ROSENBERG: Yves Rosenberg. I voted yes, no comment.

DR. KONSTAM: Mark Konstam. Yes.

DR. NEATON: Jim Neaton. Yes, nothing to add.

DR. WILSON: For those on the phone, Dr. Everett?

DR. EVERETT: I voted yes. I agree with what the others have said in terms of it being a well-conducted trial that excluded the hazard of 1.3, as it was designed to do.

DR. WILSON: Dr. Oakes?

DR. OAKES: David Oakes. I voted yes. I agree with all the other comments.

DR. WILSON: And Dr. Allegra?

DR. ALLEGRA: Carmen Allegra. I voted yes, and have no further comments.

DR. WILSON: I'm supposed to summarize 19 yeses. We heard most of those comments, but I think also one of them I mentioned in my comment is the 1.3 signal for adverse concern did not even arise in any of the subgroups that we reviewed.

The next question, this is the second voting question. I've been asked for clarification by one of the advisory committee members about this, so I will read the question, and then I'll ask the FDA about that.

Does the LEADER trial provide the substantial evidence needed to establish that liraglutide 1.8 milligrams per day reduces cardiovascular risk in patients with type 2 diabetes?

That is the voting question, or should we consider the two issues as subgroups? In fact,

then we might have two votes. And I said I believe it's going to be one vote, and they would provide a rationale.

Does that help the person who asked me that question? I know that person's in the room. The point is it's one vote, but if you feel you might have different responses to parts of this underneath, that's why you're providing your rationale. It may be tough for some people; it may not. But the point is you have one vote only. And if yes, discuss the population for whom you believe this benefit applies. If no, comment on what addition data would be needed.

DR. GUETTIER: Does anybody need additional clarification?

(No response.)

DR. GUETTIER: I think, again, in many of these questions, I think the rationale is as important as the way that you vote. So as long as you can substantiate your vote with a rationale, that would be useful for us.

DR. KONSTAM: Can I just ask -- I don't know

if anybody's going to have these feelings. There are people who have a lot of concern about the U.S. subgroup, and this is the U.S. FDA, right? And you're not asking about U.S. in this question. But if I'm sitting here and I think, well, it's a positive trial, but I just don't believe we have evidence that it works in the U.S., is that a yes vote?

DR. GUETTIER: The question really asks about substantial evidence, which is the U.S. standard for approval. The approval decision is for the U.S., and that should color your vote in terms of has the benefit been established so that it can be labeled for U.S. use.

DR. WILSON: Okay. So I believe there are no further comments or needs for clarification. We're going to vote. For those of you on the phone, we now have blinking buttons, and we're voting.

(Vote taken.)

CDR BONNER: For the record, 17 yes, 2 no, zero abstain.

DR. WILSON: All right. We're going to around in the other direction, and we'll start with Dr. Neaton. Please state your name, how you voted, and your rationale.

DR. NEATON: Jim Neaton. I voted yes. I think probably the most influential finding for me was the overall cardiovascular mortality finding, and then followed by the consistency of the results.

Concerning the target population, it's interesting. They enrolled people that had twice the risk of what they expected, so it's definitely a high-risk group. I can't offer much by way of how they would fine tune their inclusion criteria, but clearly they should be going after a very high-risk group.

DR. KONSTAM: Mark Konstam. I voted yes. I already spoke to the fact that I think the overall primary trial results are very robust and substantiated, and the cardiovascular mortality is the biggest contributor to that, which is obviously a very important finding.

I think the population is the population with established cardiovascular disease, on two counts. One is, in that other subgroup, I'm just not convinced that it contributed anything to the hazard benefit. And secondly, even if you say, well, it's a subgroup and the hazard benefit, it's got to be assumed to be the same, which I wouldn't agree with -- but if you did say that, you'd still have a much lower event rate in that group. So a lesser absolute benefit.

On both grounds, I think the population here is that with established cardiovascular disease. And I am concerned about the U.S. population, but at the end of the day, it's a subgroup, and I just can't overrate that to diminish the overall finding.

DR. ROSENBERG: Yves Rosenberg. I voted yes for similar reasons that have just been stated. These are very obvious consistent results from a statistical point of view. The interpretation of those from a clinical point of view may be a little more complicated, but that shouldn't prevent the

approval of this drug. At least if we use the same criteria that we've used for EMPA-REG, we have to be fair and recognize that the substantial evidence, the level of evidence, has been provided. These were as good if not better than we had to review previously.

Certainly, I'm concerned, as others, with how to apply the results to the U.S. population and whether or not it's related to adherence. But we have the data we have, and that justifies the labeling.

DR. DE LEMOS: James de Lemos. I also voted yes. I thought that the primary endpoint result was borderline for a standalone trial but, as we've said, buttressed by very strong results for cardiovascular and all-cause mortality. I agree with Dr. Everett that the burden is a little bit lower here since the drug is already on the market and used in these patients, so I think it meets those criteria.

I do feel strongly that they have not demonstrated benefit in the lower risk groups and

would suggest a label that said something like for cardiovascular risk reduction among individuals at high cardiovascular risk on the basis of evident or prevalent cardiovascular -- clinical or subclinical cardiovascular disease or chronic kidney disease.

I'm a little less worried by the U.S. subgroup. I think it's not really plausible, and we have other examples like PEGASUS, where anomalous findings happen in the U.S., and we've moved forward and have not looked back.

DR. WILSON: Peter Wilson. I voted yes. Primary prevention, secondary prevention, and some of the subgroups that were used in this trial are not all the same, so I've wrestled with exactly who benefits the most because of the overlapping of some of these groupings. But I think Dr. Konstam said it best. As people who really have atherosclerotic cardiovascular disease, and its clinically manifest, are probably the people who will benefit the most. And I would hope that's the people who will get the medication.

DR. FRADKIN: Judy Fradkin. I voted yes. I

thought the primary outcome was very compellingly demonstrated. I think it was demonstrated in the population that has established heart disease. I think it may well be useful in other people, but I don't think that this study proved that. So I would say we have to go with the population that was studied.

CAPT BUDNITZ: Dan Budnitz. I guess I'll be the first to vote no. This was a tough decision, but the rationale was the indication asked for is an adjunct to standard treatment in the United States for a U.S. label. So if a subgroup analysis that looks at U.S. residents versus the world isn't appropriate to do, then I don't know what subgroup analysis we should ever do.

I do worry about a slippery slope of using a single-trial data for new indications when there are questions and when you do have a significant interaction term for the U.S. versus the rest of the world.

What would I like to see? I think that's part of the question that might be for further

study. I think it would be either another international trial where the U.S. subgroup isn't different than the rest of the world, or a U.S. trial. It's pretty simple.

I think the thing to think about, that I thought about as well, is the EMPA-REG trial, which although it was not a statistically significant interaction in that trial, the U.S. subgroup was -- the point estimate was much less efficacious than the rest of the world.

So here we have two CVOTs that maybe have some concern, and I wonder if we see a third if the U.S. again is lagging in terms of the size of the point estimate of benefit or not and what folks would say about that, if we have a third trial that has the same -- if U.S. is the outlier again. Is that, again, chance alone or is there something else going on?

The last comment I'll make is I can be assuaged a little bit by this drug already being on the market. If thinking about a single trial being used to judge an indication, it might be a little

bit different circumstances, but again I worry about a slippery slope of how we're using a single trial to justify new indications.

DR. LOW WANG: This is Cecilia Low Wang. I voted yes. And I have to say that the primary endpoint, the results of that, were very convincing especially because all the components were also significant, including all-cause mortality.

I have some concerns about the U.S. subgroup, but I think that adherence may explain that, but it's hard to know. I think that this drug does seem to reduce cardiovascular risk in those patients at the very highest risk established as CVD, chronic kidney disease, and possibly heart failure as well.

I think that one of the things that this trial does highlight is the heterogeneity in patients with diabetes. We already know that even though we divide patients into type 1, type 2, 3, 4, type 2 patients are extremely heterogeneous. So I think that we need to keep that in mind as we're thinking about drug labels.

If we were to do another trial to try to broaden the label beyond the highest risk, patients with diabetes at the very highest risk, I might want to see something looking at patients with diabetes and primary prevention of ASCVD.

MS. HALLARE: Diana Hallare. I voted yes. Like Dr. de Lemos and Dr. Wilson, I agree that the benefit applies mainly to those with renal disease, as well as established cardiovascular disease. I, however, have a concern about the duration of the study for the U.S. population. It was about half the length of the duration for other populations around the world, such as in Asia and in Europe.

Also, with regards to the dosage, I would like to have it compared with other dosages. Those are my main concerns, but otherwise there were good outcomes primarily with the primary endpoint.

DR. CHO: Leslie Cho. I voted yes. I think it should have an indication for reduction of MACE in patients with established cardiovascular disease or with CKD. I think the broader indication of high cardiovascular risk in which things like LV

dysfunction, microalbuminuria, and some other things that were included in 3b is a troubling aspect of this yes vote.

DR. BURMAN: Ken Burman. I voted yes. This question requires a difficult decision in my view, as there is evidence on both sides of the issue. LEADER is a reasonable postmarketing study.

Total MACE was statistically significantly different between the two groups favoring liraglutide, as was cardiovascular deaths. However, non-fatal MIs and non-fatal strokes were not statistically different when performed individually. Angina, coronary vascularization, and CHF admissions were also not individually statistically significantly different.

There's also the issue, as has been brought up numerous times, of the U.S. component. The FDA usually requires two or more adequate trials with important endpoints. Here we are considering a single trial that probably meets the FDA criteria to be reliable, statistically significant, and have important clinical results. Thus, in my view,

allowing determination of a label on a single trial.

There are also discussions and concerns regarding possible side effects, specifically pancreatitis, pancreatic cancer, hypoglycemia, skin cancer, and possible immunogenicity. The evidence, however, is presently inconclusive and is leaning toward favoring no adverse effects in those regards.

However, it is important to have available antidiabetic agents that have been proven or are very likely to decrease cardiovascular risk and cardiovascular events. It is also important to investigate the mechanism involved in this cardiac risk decrement. We had mentioned before the populations to be appropriate, and those are high-risk cardiovascular populations, as noted.

Considering all of these factors, I think the preponderance of data supports the approval of liraglutide for the treatment of type 2 diabetes in patients with high cardiovascular risk or events, and of course further studies are warranted. Thank

you.

DR. BLAHA: Mike Blaha. I voted yes. And after great consideration, I voted really consistent with what's written in the proposed label, really, on the basis of the fact that almost everyone with diabetes and another major risk factor, if not existing cardiovascular disease, is indeed high risk, to use that term from the label. So I actually voted consistent with that label.

I thought it was a very well-done trial. I'm impressed by the hard outcomes like all of us were. We've all seen trials recently, whether it be from PCSK9 inhibitors to other lipid lowering drugs for other things, where we see effects on softer endpoints but not on hard endpoints, so that's really reassuring.

I think we're seeing an impact on hard outcomes, including all-cause death, which of course is the ultimate arbiter of an outcome. That was enough to reassure me that a single trial was enough for me to have substantial evidence, enough to vote yes.

I actually don't think another outcome trial would actually impact clinical practice all that much. So I'm not sure guideline writers and things, with having a second trial, would actually move this drug on the decision pathway all that much, nor necessarily my clinical practice. So I had a hard time recommending a second trial, and I'm not sure that that would change people's clinical approach all that much.

I do have a concern about the subgroups; we've discussed this in great detail. Ultimately, I'm siding on the side of not over-interpreting small subgroups. The U.S. subgroup was small; actually the 3b group was even smaller.

So ultimately I'm voting consistent with the label that people with diabetes that are high risk will get a cardiovascular outcome benefit from this drug.

DR. YANOVSKI: Sue Yanovski. I voted yes. I thought the reduction in MACE and cardiovascular and all-cause mortality were not only statistically significant but were agreed to be clinically

meaningful to patients.

In terms of the indication, I was among the group who really felt that this was shown in the patients with established cardiovascular disease or at highest cardiovascular risk. I'm really less compelled by the evidence of perhaps that lower risk group with a single trial. I leave that to me colleagues at FDA to figure out how one would say that or figure out who's at the highest risk.

MS. McCALL: Debra McCall. I voted yes for many of the reasons that have already been stated, but mostly -- well, primarily those by Dr. Neaton and Dr. Blaha. Also, for the obese diabetic patient, I think this is a drug that both patient and clinician need in their arsenal, particularly those that at moderate to high risk for cardiovascular disease.

DR. SANOFF: Hanna Sanoff. I also voted yes. It wasn't without some concern though. Principally, I think the hazard ratio is unequivocally in favor of the drug for reducing cardiovascular events, but we haven't spent a lot

of time talking about the clinical relevance of that. The absolute risk reduction here is exceptionally small in terms of cardiovascular reduction.

That said, it is positive, and it's a drug that is already used for other indications and had a very good safety signal, in my opinion, with regard to some of the special outcomes of concern. So that allayed my concern that the absolute risk reduction was not significant.

As a comparative effectiveness researcher, I actually have a lot of concern about the generalizability of these data for Americans, and I think that may speak somewhat to the U.S. subpopulation concerns.

This trial had a lot of dropout in terms of the run-in period of people unable to do injections, and we saw the U.S. patients who were unable to stay on the drug for a long time. So the impassioned arguments for using this for our patients who need it, maybe a lot of them aren't going to get this benefit.

That said, I've felt as though, as many folks have voiced before, this is a drug that is already approved. It showed a robust outcome in terms of cardiovascular reduction, albeit clinical significance from an individual person's perspective, not a population perspective. But, for the patient sitting in front of you, I think frankly it's probably fairly marginal.

DR. ROBBINS: David Robbins. I voted yes. This was not a slam-dunk. I think the subgroup analysis was an interesting discussion, but in the end, I think you have to take the data and the primary outcome measure as what you move on.

I think in the end, my faith is in the informed consumer. I think that the innuendos of this study will be clear, and like many things in medicine, it's not black and white, and people will be able to see through that. So I think the good is outweighing the bad in this. I certainly am glad to see diabetes moving towards more than lowering the blood sugar, and I think that's a good step in the right direction.

DR. WILSON: Thank you.

Dr. Everett, would you please state your name, your vote, and your rationale for your vote?

DR. EVERETT: Hi. This is Brendan Everett. I voted yes. The rationale was similar to what many others have said before me, but essentially I think that having a diabetes drug that has an important benefit on cardiovascular endpoints, and in particular cardiovascular mortality, is a huge breakthrough for clinicians and patients alike.

I think LEADER was a well-conducted trial. As we've all said many times, the consistency of the effect of the study drug across the various cardiovascular endpoints is reassuring. In particular, I think you have to pay close attention when there's a signal for cardiovascular and all-cause mortality.

I actually feel that the absolute risk reduction is more substantial or more clinically meaningful than perhaps some others on the panel do, and that's because we've spent years and years treating blood sugar with zero effect on absolute

risk, and now we potentially have two agents that can give us an effect on the absolute risk of a very important endpoint, namely death.

That said, I think that the population where this drug should be used or should be approved for use is among those with either clinical or cardiovascular disease, or if not clinical, then important subclinical disease such as known non-obstructive coronary disease for example, and perhaps chronic kidney disease as well because I think that's the population where the benefit is likely to be most apparent.

Whether or not the evidence is substantial I think is the most difficult call. I have trouble with this being one trial because a repeat trial might not quite get us to the level of statistical significance. But remembering my feelings and my vote from a similar meeting a year ago, I felt it to be intellectually consistent with the way I felt at that time, that this was also a yes in terms of approving the label. So I'll stop there.

DR. WILSON: Dr. Oakes?

DR. OAKES: David Oakes. I voted yes. Again, I agree with the reasons that have been given. I would make the recommendation that others have made, that FDA review the proposed labeling in regard to CV history.

I also feel that the fact that the efficacy finding was driven more by the non-U.S. than the U.S. population, or some such similar wording, should be included in the package insert so people can make their own judgement as to the significance of that.

DR. WILSON: Dr. Allegra?

DR. ALLEGRA: Carmen Allegra. I was the other minority vote of no. I was very much concerned and swayed by the subgroup analysis. I think the U.S. target population is a pretty darn important population for us to consider, and we saw a significant interaction with outcomes versus the region by the FDA's analysis. It's not a small population of patients; it was a substantial population given that it was a significant percentage of the total, which was a huge study, at

least from the cancer perspective.

So I was really swayed by the fact that we really didn't see evidence for superiority in the U.S. population, and yet in other parts of the world, even in smaller populations that were included in the trial, we still saw a superiority, or at least most of the points were to the left of unity, even though the confidences were a little bit broader and may have crossed unity.

I'm not so sure that it's important to understand why it is that the U.S. population seems to be different. It certainly was I thought somewhat convincing that maybe the population wasn't exposed to enough of the drug. But whether the U.S. population can't or won't take the agent for whatever reason, or there's differences in practice in the U.S. versus rest of the world, the fact is that we just don't see good evidence. And again, as others pointed out, it's a single trial.

So what would I like to see? I would be convinced if I saw a superiority trial in U.S. population. I don't know that that's a

particularly practical thing to do, and I don't know if I would advocate doing that, particularly since the agent's already approved and it's out there being used. And I suppose if the labeling is clear about this concern of efficacy in the U.S., then I guess I'd be reasonably content with that. But I don't think it's fair to make a blanket approval here and say this is good for the U.S. patients because we really don't see evidence of that. And I'll go ahead and stop there.

DR. WILSON: I think that's the end of all of our voting and all of our discussion. The last word comes from the FDA our hosts, Jean-Marc and colleagues?

DR. GUETTIER: I'd like to thank everybody for their participation today, and especially some of the members that got up at 3:00 a.m. this morning to actually get on the flight to be here in person. I think it was quite an ordeal for a lot of people to get here. We appreciate all the people that actually were willing to participate by phone today, as well. I know it's harder to

actually follow the meeting by phone. And we got a lot of good feedback from all the advisors today, so thank you very much.

Adjournment

DR. WILSON: Just as a final reminder, take your personal belongings. Any papers you leave here will be disposed of, so don't worry about that. You can recycle your name badge; leave it on the desk or outside.

(Whereupon, at 4:41 p.m., the meeting was adjourned.)