1   FOOD AND DRUG ADMINISTRATION

2   CENTER FOR DRUG EVALUATION AND RESEARCH

3

4

5   ENDOCRINOLOGIC AND METABOLIC DRUGS

6   ADVISORY COMMITTEE (EMDAC) MEETING

7

8

9   Tuesday, June 28, 2016

10   7:59 a.m. to 4:43 p.m.

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16   Hilton Washington DC/Rockville

17   Hotel & Executive Meeting Center Plaza Ballroom

18   1750 Rockville Pike

19   Rockville, MD 20852

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# Meeting Roster

**DESIGNATED FEDERAL OFFICER (Non-Voting)**

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Division of Advisory Committee and Consultant

Management

Office of Executive Programs, CDER, FDA


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3    Harvard Medical School

4    Director, General Cardiology Inpatient Service

5    Brigham and Women's Hospital

6    Boston, Massachusetts

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8    **Diana Hallare, MPH**

9    *(Consumer Representative)*

10   Visalia, California

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12   **Susan R. Heckbert, MD, PhD**

13   Professor

14   Department of Epidemiology

15   University of Washington

16   Cardiovascular Health Research Unit

17   Seattle, Washington

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3    University of Colorado School of Medicine

4    President CPC Clinical Research

5    Aurora, Colorado

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7    **James D. Neaton, PhD**

8    Professor of Biostatistics

9    Division of Biostatistics

10   School of Public Health

11   University of Minnesota

12   Minneapolis, Minnesota

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14   **Robert J. Smith, MD**

15   *(Chairperson)*

16   Professor of Medicine (Endocrinology)

17   The Warren Alpert School of Medicine

18   Professor of Health Services, Policy and Practice

19   Brown University

20   Providence, Rhode Island

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1    **Peter W. F. Wilson, MD**

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3    Epidemiology and Genomic Medicine

4    Atlanta Veterans Administration Medical Center

5    Professor of Medicine and Public Health

6    Emory University

7    Emory Clinical Cardiovascular Research Institute

8    Atlanta, Georgia

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10   **Susan Z. Yanovski, MD**

11   Co-Director, Office of Obesity Research

12   Senior Scientific Advisor for Clinical Obesity

13   Research

14   National Institute of Diabetes and Digestive and

15   Kidney Diseases (NIDDK)

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17   Bethesda, Maryland

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**ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY**

**COMMITTEE MEMBER (Nonvoting)**

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Professor and Chair

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Penn State Milton S. Hershey Medical Center

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**Marvin A. Konstam, MD**

Professor of Medicine, Tufts University

Chief Physician Executive

The Cardiovascular Center, Tufts Medical Center

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1  **Melissa Li-Ng, MD**

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3  Cleveland Clinic Abu Dhabi

4  Abu Dhabi, United Arab Emirates

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8  Cleveland, Ohio

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10  **Richard Lumley, EdD**

11  *(Patient Representative)*

12  Kansas City, Missouri

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14  **Kevin D. McBryde, MD**

15  Medical Officer, Division of Extramural Research

16  National Institute of Dental and Craniofacial

17  Research, NIH

18  Bethesda, Maryland

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**Paul Palevsky, MD**

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VA Pittsburgh Healthcare System

Professor of Medicine and Clinical & Translational

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Branch Chief, Atherothrombosis and Coronary

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Adult and Pediatric Cardiac Research Program

Division of Cardiovascular Services

National Heart, Lung, Blood Institute, NIH

Bethesda, Maryland

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3   University of California San Francisco

4   San Francisco, California

5

6   **Abraham Thomas, MD, MPH**

7   Senior Vice President and Chair

8   Department of Medicine

9   New York University Lutheran

10  Brooklyn, New York

11

12  **FDA PARTICIPANTS (Non-Voting)**

13  **Jean-Marc Guettier, MD**

14  Director, Division of Metabolism and Endocrinology

15  Products (DMEP)

16  Office of Drug Evaluation II (ODE-II)

17  Office of New Drugs (OND), CDER, FDA

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19  **Norman L. Stockbridge, MD, PhD**

20  Director

21  Division of Cardiovascular and Renal Products

22  ODE-I, OND, CDER, FDA

1  **William H. Chong, MD**

2  Clinical Team Lead

3  DMEP, ODE-II, OND, CDER, FDA

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5  **Jennifer Clark, PhD**

6  Mathematical Statistician

7  Division of Biometrics II, Office of Biostatistics

8  Office of Translational Sciences, CDER, FDA

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10  **Andreea Lungu, MD**

11  Clinical Reviewer

12  DMEP, ODE II, OND, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

1                  P R O C E E D I N G S

2                    (7:59 a.m.)

3                  **Call to Order**

4             **Introduction of Subcommittee**

5         DR. SMITH:  Good morning again.  I would

6 like to start out by reminding everyone to please

7 silence your cell phones, smartphones, or any other

8 devices if you have not already done so.  And I

9 would also like to identify the FDA press contact,

10 Theresa Eisenman; if you are present, Theresa, in

11 the back with her hand up.

12        My name is Robert Smith.  I am the

13 Chairperson of the Endocrinologic and Metabolic

14 Drugs Advisory Committee, and I will be chairing

15 this meeting.  I will now call the Endocrinologic

16 and Metabolic Drugs Advisory Committee Meeting to

17 order.  We'll start by going around the table and

18 introduce ourselves.  We will start with the FDA to

19 my left and then proceed around the table.

20        DR. GUETTIER:  My name is Jean-Marc

21 Guettier.  I'm the division director in the

22 Division of Metabolism and Endocrinology Products

1  at the FDA.

2  DR. CHONG:  William Chong.  I'm the clinical

3  team leader in the Division of Metabolism and

4  Endocrine Products.

5  DR. LUNGU:  Andreea Lungu, a clinical

6  reviewer, Division of Metabolism and Endocrinology

7  Products.

8  DR. STOCKBRIDGE:  Good morning.  I'm Norman

9  Stockbridge from the Division of Cardiovascular and

10  Renal Products at FDA.

11  DR. SCHAMBELAN:  I'm Morrie Schambelan,

12  professor of medicine, Division of Endocrinology,

13  University of California San Francisco.

14  DR. BUDNITZ:  Dan Budnitz with the

15  medication safety program at the Centers for

16  Disease Control and Prevention.

17  DR. COOKE:  David Cooke.  I'm an associate

18  professor of pediatrics and the acting director of

19  pediatric endocrinology at the Johns Hopkins

20  University School of Medicine.

21  DR. NEATON:  Good morning.  Jim Neaton,

22  professor of biostatistics, University of

1    Minnesota.

2         DR. CHO:  Leslie Cho, director of women's

3    cardiovascular center and section head of

4    preventive cardiology at Cleveland Clinic.

5         DR. FRADKIN:  Judy Fradkin, director of the

6    Division of Diabetes, Endocrinology and Metabolic

7    Diseases at the National Institute of Diabetes and

8    Digestive and Kidney Diseases, NIH.

9         DR. ROSENBERG:  Good morning.  My name is

10   Yves Rosenberg.  I'm the chief of the

11   atherothrombosis and coronary artery disease branch

12   in the Division of Cardiovascular Sciences at the

13   National Heart, Lung, and Blood Institute, the NIH.

14        DR. MCBRYDE:  Good morning.  My name is

15   Kevin McBryde.  I'm a pediatric nephrologist and a

16   medical officer at the National Institute of Dental

17   and Craniofacial Research at the NIH.

18        DR. EVERETT:  Good morning.  I'm Brendan

19   Everett.  I'm the director of the General

20   Cardiology Inpatient Service at the Brigham and

21   Women's Hospital and assistant professor of

22   medicine at Harvard Medical School.

1          DR. BONNER:  Good morning.  LaToya Bonner,

2     designated federal officer for this meeting.

3          DR. SMITH:  I'm Robert Smith.  I'm a

4     diabetes and endocrinology clinician and

5     researcher.  I'm a professor in medicine, and also

6     in the School of Public Health at Brown University.

7          DR. THOMAS:  Abraham Thomas, chief of

8     medicine, NYU Lutheran, and vice chair of medicine,

9     NYU School of Medicine.

10          DR. KONSTAM:  Marv Konstam.  I direct the

11     cardiovascular center at Tufts Medical Center in

12     Boston.

13          DR. LI-NG:  Melissa Li-Ng, consultant

14     endocrinologist, Cleveland Clinic Abu Dhabi.

15          DR. GOOD:  Good morning.  I'm David Good,

16     professor and chair of neurology at Penn State

17     College of Medicine.

18          DR. DE LEMOS:  James De Lemos, cardiologist

19     and professor of medicine at UT Southwestern in

20     Dallas.

21          MS. HALLARE:  Good morning.  Diana Hallare,

22     consumer representative.

1          DR. PALEVSKY:  I'm Paul Palevsky.  I'm a

2    nephrologist, professor of medicine at the

3    University of Pittsburgh School of Medicine and

4    chief of renal at the Pittsburgh VA.

5          DR. WILSON:  Peter Wilson, professor of

6    endocrinology and preventive cardiology and public

7    health at Emory.

8          DR. HECKBERT:  Susan Heckbert, professor in

9    epidemiology, University of Washington, Seattle.

10          DR. YANOVSKI:  Susan Yanovski.  I co-direct

11    the Office of Obesity Research at the National

12    Institute of Diabetes and Digestive and Kidney

13    Diseases.

14          MR. LUMLEY:  Dan Lumley, patient rep from

15    Kansas City.

16          DR. HIATT:  William Hiatt, professor of

17    medicine, University of Colorado, Division of

18    Cardiology where I practice vascular medicine.

19          DR. PROSCHAN:  I'm Michael Proschan.  I'm a

20    mathematical statistician at the National Institute

21    of Allergy and Infectious Diseases.

22          DR. KEWALRAMANI:  Reshma Kewalramani.  I'm a

1    nephrologist and I head the U.S. medical

2    organization at Amgen.  I'm the industry

3    representative.

4         DR. SMITH:  Thank you.  For topics such as

5    those being discussed at today's meeting there are

6    often a variety of opinions, some of which are

7    quite strongly held.  Our goal is that today's

8    meeting will be a fair and open forum for

9    discussion of these issues, and that individuals

10   can express their views without interruption.

11   Thus, as a gentle reminder, individuals will be

12   allowed to speak into the record only if recognized

13   by the chairperson.  We look forward to a

14   productive meeting.

15        In the spirit of the Federal Advisory

16   Committee Act and the Government in the Sunshine

17   Act, we ask that the advisory committee members

18   take care that their conversations about the topic

19   at hand take place in the open forum of the

20   meeting.

21        We are aware that members of the media are

22   anxious to speak with the FDA about these

1 proceedings, however, FDA will refrain from

2 discussing the details of this meeting with the

3 media until its conclusion.  Also, the committee is

4 reminded to please refrain from discussing the

5 meeting topic during breaks or lunch.  Thank you.

6 　　　　Now, I'll pass the microphone to Commander

7 LaToya Bonner, who will read the conflict of

8 interest statement.

9 **Conflict of Interest Statement**

10 　　　　DR. BONNER:  The Food and Drug

11 Administration is convening today's meeting of the

12 Endocrinologic and Metabolic Drug Advisory

13 Committee under the authority of the Federal

14 Advisory Committee Act of 1972.  With the exception

15 of the industry representative, all members and

16 temporary voting members of the committee are

17 special government employees or regular federal

18 employees from other agencies and are subject to

19 federal conflict of interest laws and regulations.

20 　　　　The following information on the status of

21 this committee's compliance with federal ethics and

22 conflict of interest laws, covered by but not

1    limited to those found at 18 U.S.C., Section 208,

2    is being provided to participants in today's

3    meeting and to the public.

4         FDA has determined that members and

5    temporary voting members of this committee are in

6    compliance with federal ethics and conflict of

7    interest laws.  Under 18 U.S.C., Section 208,

8    Congress has authorized FDA to grant waivers to

9    special government employees and regular federal

10   employees who have potential financial conflicts

11   when it is determined that the agency's need for a

12   special government employee's services outweighs

13   his or her potential financial conflict of

14   interest, or when the interest of a regular federal

15   employee is not so substantial as to be deemed

16   likely to affect the integrity of the services

17   which the government may expect from the employee.

18        Related to the discussion of today's

19   meeting, members and temporary voting members of

20   the committee have been screened for potential

21   financial conflicts of interest of their own, as

22   well as those imputed to them, including those of

1   their spouses or minor children, and for purposes

2   of 18 U.S.C., Section 208, their employers.  These

3   interests may include investments, consulting,

4   expert witness testimony, contracts, grants,

5   CRADAs, teaching, speaking, writing, patents and

6   royalties, and primary employment.

7        Today's agenda involves supplemental new

8   drug application 204629 for empagliflozin tablets,

9   and supplemental new drug application 206111 for

10  empagliflozin and metformin hydrochloride tablets.

11  Both sNDAs are sponsored by Boehringer Ingelheim

12  Pharmaceuticals, Incorporated, for the proposed

13  additional indication in adult patients with type 2

14  diabetes mellitus and high cardiovascular risk to

15  reduce the risk of all-cause mortality by reducing

16  the incidence of cardiovascular death and to reduce

17  the risk of cardiovascular death or hospitalization

18  for heart failure.

19       This is a particular matters meeting during

20  which specific matters related to Boehringer

21  Ingelheim's sNDAs will be discussed.  Based on the

22  agenda for today's meeting and all financial

1    interests reported by the committee members and

2    temporary voting members, a conflict of interest

3    waiver has been issued in accordance with 18 U.S.C.

4    Section 208(b)(3) to Dr. Marvin Konstam.

5         Dr. Konstam's waiver addresses his

6    employer's contract with a potentially competing

7    firm regarding a product that potentially will

8    compete with the products under review by the

9    committee.  The total funding is anticipated to be

10   between zero and $50,000 per year.  Dr. Konstam

11   will not have any role in the actual conduct of the

12   study.

13        The waiver allows this individual to

14   participate fully in today's deliberations.  FDA's

15   reason for issuing the waiver are described in the

16   waiver documents, which are posted on the FDA

17   website at www.fda.gov/AdvisoryCommittees/

18   CommitteesMeetingMaterials/Drugs/default.htm.

19        Copies of the waiver may also be obtained by

20   submitting a written request to the agency's

21   Freedom of Information Division, on 5630 Fishers

22   Lane, Room 1035, Rockville, Maryland 20857, or

1    requests may be sent via fax to 301-827-9267.

2         To ensure transparency, we encourage all

3    standing committee members, and temporary voting

4    members, to disclose any public statements that

5    they have made concerning the product at issue.

6         With respect to FDA's invited industry

7    representative, we would like to disclose that Dr.

8    Reshma Kewalramani is participating in this meeting

9    as a non-voting industry representative acting on

10   behalf of regulated industry.  Dr. Kewalramani's

11   role at this meeting is to represent industry in

12   general and not any particular meeting [sic].  Dr.

13   Kewalramani is employed by Amgen.

14        We would like to remind members and

15   temporary voting members that if the discussion

16   involve any other products or firms not already on

17   the agenda for which an FDA participant has a

18   personal or imputed financial interest, the

19   participants need to exclude themselves from such

20   involvement and their exclusion will be noted for

21   the record.  FDA encourages all other participants

22   to advise the committee of any financial

1    relationships that they may have with the firm at

2    issue.  Thank you.

3         DR. SMITH:  Thank you.  So, we'll now

4    proceed with the FDA's introductory remarks from

5    Dr. Jean-Marc Guettier.

6                **FDA Introductory Remarks**

7         DR. GUETTIER:  Is it possible to project the

8    slides on the screen?  Good morning.  My name is

9    Jean-Marc Guettier, and I'm the director of the

10   Division of Metabolism and Endocrinology Products

11   at the Food and Drug Administration.  I'd like to

12   welcome all of the meeting participants and the

13   panel members to today's advisory committee

14   meeting, which was convened to review the results

15   of the EMPA-REG OUTCOME study.

16        The EMPA-REG OUTCOME study was required by

17   the Food and Drug Administration to evaluate the

18   cardiovascular risk associated with the use of

19   empagliflozin for the treatment of adults with

20   type 2 diabetes.  Recall that all anti-diabetic

21   therapies are indicated as an adjunct to diet and

22   exercise, and are used to improve glycemic control.

         The regulatory context demonstrating an

improvement in glycemic control over the medium

term serves as a surrogate for microvascular

disease risk reduction and for full approval of

these agents.  To date, no prospectively planned

study has convincingly demonstrated a link between

improvement in glycemic control and reduction in

cardiovascular risk.

         The EMPA-REG OUTCOME study is the first

large, dedicated, randomized, prospective,

controlled outcomes trial to report on a

cardiovascular benefit of a specific anti-diabetic

therapy.

         Several other anti-diabetic agents have been

evaluated in similarly designed studies, and until

the publication of the EMPA-REG OUTCOME study, no

anti-diabetic agent had been shown to reduce

cardiovascular risk.

         The results of the EMPA-REG OUTCOME study

are thus a departure from previous scientific

findings, and represent a potentially important

advance in the treatment of adults with type 2

1   diabetes.

2        The committee was convened to discuss

3   whether the results of the study established that

4   empagliflozin is effective at reducing

5   cardiovascular risk in adult patients with type 2

6   diabetes, and in so doing advise the agency with

7   regards to adding a potentially new use to the

8   product label.

9        The indication submitted when the

10  supplemental application was filed in November is

11  the first indication shown on this slide.  This was

12  the working indication FDA was asked to consider,

13  and the indication published in the Federal

14  Register notice for this meeting.

15       The indication reads, "Empagliflozin is

16  indicated in adult patients with type 2 diabetes

17  mellitus and high cardiovascular risk to reduce the

18  risk of all-cause mortality by reducing the

19  incidence of cardiovascular death, and to reduce

20  the risk of cardiovascular death or hospitalization

21  for heart failure."

22       In early May, the applicant submitted an

1    amendment to the application to have the proposed

2    indication changed to the following.

3         "In adult patients with type 2 diabetes

4    mellitus and established cardiovascular disease,

5    empagliflozin is indicated to reduce the incidence

6    of cardiovascular death."  This new indication is

7    the current working version and reflects the new

8    use the applicant is seeking.

9         Since you will be asked to opine on whether

10   the study results establish the efficacy of

11   empagliflozin for a new use, let me briefly review

12   FDA requirements regarding the evidence needed to

13   form the basis for a new efficacy claim.  The legal

14   standard of effectiveness to support a new use of

15   an approved product is described in the Federal

16   Food, Drug, and Cosmetic Act as substantial

17   evidence of effectiveness.

18        In the law, substantial evidence is defined

19   as evidence consisting of adequate and

20   well-controlled investigations, including clinical

21   investigations, that the drug has the effect it

22   purports or is represented to have under the

1  condition of use prescribed in the labeling or

2  proposed labeling thereof.  The adequate and

3  well-controlled statement speaks to the quality of

4  the evidence required, and this will be reviewed in

5  a following slide.

6        With regards to the quantity of evidence

7  necessary, the law talks about investigations in

8  the plural form, and it has been FDA's position

9  that Congress generally intended to require at

10  least two adequate and well-controlled studies,

11  each convincing on its own, to establish

12  effectiveness and support approval of a new use.

13        The scientific basis for requiring two

14  studies is grounded in the fact that chance,

15  biases, biologic variability, generalizability

16  issues for other factors inherent to the single

17  positive trial, could lead to an erroneous

18  conclusion that the drug is effective when in fact

19  it is not.

20        Simply stated, a conclusion based on two

21  persuasive studies will always be more secure than

22  a conclusion based on a single comparatively

1    persuasive study.  We will return to this concept

2    in a later slide, but let me first briefly cover

3    issues related to the quality of the evidence

4    required.

5            With regards to the quality of the evidence,

6    the applicant has to demonstrate that the studies

7    were adequately designed and conducted.  General

8    attributes of an adequate and well-controlled trial

9    are described in Title 21 of the Code of Federal

10    Regulations and are summarized in this slide.

11            To demonstrate that the trial supporting an

12    effectiveness claim is adequate and

13    well-controlled, extensive documentation related to

14    trial planning, trial conduct and data handling is

15    needed.  Records of this extensive documentation

16    are submitted to the agency for review, and

17    detailed patient records at the clinical sites

18    participating in the study are made available for

19    the purpose of auditing.

20            This morning Dr. Lungu will spend some time

21    reviewing the complex regulatory history for the

22    EMPA-REG study, which is in many ways unique, and

1    will summarize the major changes to the protocol,

2    clinical endpoint charter, and analysis plan made

3    during trial conduct.  You will be asked to

4    consider these changes in your discussion this

5    afternoon when weighing the quality of the evidence

6    generated by the EMPA-REG study.

7            Let me return to the issues surrounding the

8    quantity of evidence necessary to support a new

9    claim.  Although, as stated earlier, two adequate

10   and well-controlled studies are generally needed to

11   form the basis of an effectiveness claim, the FDA

12   has recognized that there are certain circumstances

13   when a single study could constitute substantial

14   evidence.

15           In 1997 the Federal Food, Drug, and Cosmetic

16   Act was amended to make it clear that the agency

17   may consider data from one adequate and

18   well-controlled clinical investigation and

19   confirmatory evidence to constitute substantial

20   evidence if FDA determines that such data and

21   confirmatory evidence are sufficient to establish

22   effectiveness.

1          Indeed, FDA has at times relied on a single

2     adequate and well-controlled efficacy study to

3     support approval of a new drug or a new use.  This

4     has generally occurred only in cases in which a

5     single multi-center study of excellent design

6     provided highly reliable and statistically strong

7     evidence of an important clinical benefit.

8          Whether to rely on a single adequate and

9     well-controlled study to form the basis of a claim

10    is inevitably a matter of judgment.  And as stated

11    previously, a conclusion based on two persuasive

12    studies will always be more secure than a

13    conclusion based on a single similarly persuasive

14    study.

15         The agency's views on when a single trial

16    could serve as the basis to conclude that

17    substantial evidence has been met is described in a

18    guidance document.  In this document, the agency

19    identifies some characteristics of a single

20    adequate and well-controlled study that can

21    contribute to a conclusion that the single study

22    would be adequate to form the basis of a new

1    efficacy claim.  These characteristics are shown on

2    this slide.

3          Although the list is not exhaustive and no

4    one single characteristic is necessarily

5    determinative, the presence of one or more of these

6    in a study may provide support to reach a

7    conclusion that the study is adequate.

8          In your deliberations this afternoon, we

9    will ask you to keep these characteristics in mind

10    as you are weighing whether the single EMPA-REG

11    study provides the necessary substantial evidence

12    of effectiveness to support a new claim.

13          Having briefly reviewed the expectations

14    regarding both the quality and the quantity of

15    evidence needed to form the basis of a new claim,

16    let me present the charge to the committee.

17          The committee was convened today to review

18    the evidence generated in the EMPA-REG study and

19    advise the agency on whether the study provides

20    substantial evidence of effectiveness required to

21    form the basis of a new claim for empagliflozin.

22    The focus of this afternoon's discussion will

1    tackle this objective, so let me turn to the

2    discussion points.

3       The first discussion point focuses on the

4    quality of the evidence. The trial has had a

5    complex regulatory history and several changes were

6    implemented during trial conduct. This will be

7    discussed in details this morning.

8       In addition, some sponsor unblinding

9    occurred to support an interim analysis required

10    for the purpose of regulatory filing, and this is

11    unique to this trial. In this question, we ask

12    whether specifics of the study conduct alter or do

13    not alter your level of confidence in the main

14    study findings.

15       The second discussion point focuses on the

16    persuasiveness of the results for the primary

17    analysis, and asks you to comment on several

18    issues, including the persuasiveness of the

19    statistical results, the findings across each

20    individual component to the primary composite

21    endpoint, and specifically on the topic of silent

22    myocardial infarctions.

1    These issues will be covered in our

2   presentation and we would like your opinion on how

3   these factors influence your confidence in the

4   results of the primary analysis.

5        The third discussion point focuses

6   specifically on the persuasiveness of the mortality

7   findings.  While the discussion of mortality is

8   certainly not limited to the issues listed here, we

9   will be covering these issues in our presentation,

10  and would like you to address these specifically in

11  your discussion.

12       Discussion point number 4 relates to the

13  heart failures finding in the EMPA-REG OUTCOME

14  study.  And discussion point number 5 relates to

15  the renal endpoint findings in the EMPA-REG OUTCOME

16  study. Specifically, it asks whether the changes in

17  the endpoint establish a benefit of the drug on

18  kidney disease related to diabetes.

19       The first voting question asks whether the

20  EMPA-REG OUTCOME study results have fulfilled the

21  recommendations laid out in the 2008 guidance for

22  industry.  Almost as important as your vote is the

1  rationale for your vote.  We would like you to

2  explain why you voted the way you did on this

3  question.

4       The second and final voting question asks

5  whether the results of the EMPA-REG OUTCOME study

6  provides the substantial evidence of effectiveness

7  necessary to establish that empagliflozin reduces

8  cardiovascular mortality in the population studied.

9  Again, we would like you to explain the rationale

10  for your vote.

11       This concludes my introduction.  Thank you

12  and I look forward to a productive meeting.

13       DR. SMITH:  Thank you.  Both the Food and

14  Drug Administration, the FDA, and the public

15  believe in a transparent process for information

16  gathering and decision-making.  To ensure such

17  transparency at the advisory committee meeting, FDA

18  believes that it is important to understand the

19  context of an individual's presentation.

20       For this reason, FDA encourages all

21  participants, including the applicant's

22  non-employee presenters, to advise the Committee of

1       any financial relationships that they may have with

2       the applicant, such as consulting fees, travel

3       expenses, honoraria, and interests in a sponsor,

4       including equity interests and those based upon the

5       outcome of the meeting.

6              Likewise, FDA encourages you at the

7       beginning of your presentation to advise the

8       committee if you do not have any such financial

9       relationships.  If you choose not to address this

10      issue of financial relationships at the beginning

11      of your presentation, it will not preclude you from

12      speaking.

13             We will now proceed with Boehringer

14      Ingelheim Pharmaceuticals' presentations.

15      **Applicant Presentation – Hans-Juergen Woerle**

16             DR. WOERLE:  Good morning.  My name is

17      Hans-Juergen Woerle.  I'm an endocrinologist and

18      vice president of therapeutic area metabolism at

19      Boehringer Ingelheim.  The EMPA-REG OUTCOME trial

20      was conducted as a postmarketing commitment to the

21      FDA following the approval of empagliflozin for

22      glucose lowering.

1          As a sponsor, we would like to thank the FDA

2     for this opportunity to present the data from this

3     trial.  Our presentation will follow this outline;

4     study design, effects on MACE, effects on

5     cardiovascular death, effects on heart failure

6     outcome, and all-cause mortality, safety profile,

7     data integrity, and finally the clinical relevance

8     of the trial results.

9          Professor Zinman, the chair of the EMPA-REG

10    OUTCOME trial steering committee, will now discuss

11    the context and background.

12         **Applicant Presentation – Bernard Zinman**

13         DR. ZINMAN:  Thank you, Dr. Woerle.  My

14    duality of interests have been submitted.  And just

15    to repeat, I do receive consulting and grant

16    support from Boehringer Ingelheim.

17         Good morning.  As shown on this slide, the

18    prevalence of diabetes has been steadily increasing

19    in the United States.  Of note, in the age groups

20    studied in the EMPA-REG OUTCOME trial, the

21    prevalence of diabetes has actually doubled.  This

22    comes at a considerable human and healthcare cost.

1    Compared with those without diabetes, patients with

2    diabetes have a 70 percent higher risk of

3    cardiovascular mortality.

4         Having a diagnosis of diabetes decreases

5    life expectancy by six years, driven largely by

6    premature cardiovascular death.  A prior history of

7    myocardial infarction or stroke doubles this loss

8    of life to 12 years.  Thus, developing strategies

9    to modify this unacceptable outcome remains an

10   important goal in the management of diabetes.

11        A frequently less-recognized cardiac

12   comorbidity of type 2 diabetes is heart failure.

13   Heart failure is highly prevalent in patients with

14   diabetes, occurring in more than one in five

15   patients above the age of 65.

16        Patients with diabetes and heart failure

17   have a very poor prognosis, with a median survival

18   of less than five years.  It is noteworthy that no

19   glucose-lowering medication has been shown to

20   improve heart failure outcomes, while some, namely

21   thiazolidinediones, are associated with an

22   increased heart failure risk.

1       It is now well accepted, as you heard, that

2   hemoglobin A1c lowering reduces microvascular

3   complications.  A 1 percent decrease in hemoglobin

4   A1c is associated with a 37 percent reduction in

5   microvascular complications.  However, there is

6   limited evidence that reduction in hemoglobin A1c

7   results in cardiovascular outcome benefits.

8       Previous randomized trials comparing more

9   intensive with less intensive glucose lowering

10  showed no general reduction in cardiovascular

11  events or mortality in type 2 diabetes.  In fact,

12  one of the trials, the ACCORD trial, showed an

13  increase in mortality with intensive glycemic

14  therapy.

15      Data from these four trials have been pooled

16  together in a meta-analysis.  This forest plot

17  demonstrates the absence of a general benefit of

18  glycemic control on cardiovascular outcomes.

19  Stroke, shown in the first row, was not impacted.

20      There was a modest reduction in non-fatal

21  myocardial infarction.  However, the hazard ratio

22  for heart failure outcomes was one, and no

1    reduction was observed in all-cause mortality or

2    cardiovascular death.

3         The uncertainty around the cardiovascular

4    risks and benefits of glucose-lowering therapies

5    led to the development of the 2008 cardiovascular

6    guidance.  This FDA guidance set the scene for

7    recent cardiovascular outcome trials, and the

8    strategy of investigating drug-specific effects

9    through placebo-controlled trials.

10        In these trials, study drug is added to

11   standard of care, aiming for glycemic equipoise in

12   patients at high cardiovascular risk, with at least

13   two years of follow-up and with prospective

14   independent and blinded cardiovascular

15   adjudication.

16        Non-inferiority can be concluded if the

17   upper bound of the confidence interval is less than

18   1.3.  Superiority can be concluded if the upper

19   bound is less than 1.0.  In the rest of the

20   presentation today, you will see results from our

21   trial that follows this guidance.

22        Empagliflozin has been hypothesized to

1    reduce cardiovascular risk through multiple

2    mechanisms.  The primary target of empagliflozin is

3    the kidney where it increases sodium and glucose

4    excretion resulting in an osmotic diuresis.  This

5    leads to a reduction in hemoglobin A1c and weight.

6    The hemodynamic effects of decreasing intravascular

7    volume results in decreased systolic blood

8    pressure, and an increase in hematocrit.

9         Importantly, these hemodynamic effects are

10   not associated with a corresponding increase in

11   sympathetic tone.  In turn, these effects could

12   potentially decrease cardiac wall stress, minimize

13   the risk of new or worsening heart failure, and

14   reduce the risk of cardiovascular death.

15        In this context, results from the EMPA-REG

16   OUTCOME trial represents a new paradigm in the

17   treatment of diabetes.  For the first time,

18   physicians and patients have a drug that not only

19   controls metabolic parameters, but also decreases

20   the risk of cardiovascular mortality.

21        Dr. Woerle will now take you through the

22   design of our trial.

**Applicant Presentation – Hans-Juergen Woerle**

DR. WOERLE:  Empagliflozin is a highly selective inhibitor of sodium glucose co-transporter 2 in the kidney.  In the United States, it's indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.  Two doses are approved, 10 and 25 milligram per day.

In our clinical development program for empagliflozin we studied more than 13,000 patients with type 2 diabetes.  In these trials, we saw reductions in HbA1c, weight and blood pressure. The EMPA-REG OUTCOME trial was designed to meet the postmarketing requirement to conduct a randomized, double-blind, placebo-controlled trial, evaluating the effect on major cardiovascular events.  Key results of this trial are summarized in the next slide.

Empagliflozin demonstrated cardiovascular safety with the upper bound of the confidence interval being below 1.3, thus fulfilling FDA postmarketing requirements.  We had a statistically

1  significant reduction in the primary endpoint.

2  MACE, the composite of cardiovascular death, non-

3  fatal MI, and non-fatal stroke was reduced by 14

4  percent.  There was a 38 percent risk reduction in

5  cardiovascular death.  This cardiovascular

6  mortality benefit drove the reduction in MACE with

7  no significant changes in the risk of myocardial

8  infarction or stroke.

9       The reduction in cardiovascular death was

10  meaningful enough to be translated into a

11  reduction, even in all-cause mortality, by 32

12  percent.  Heart failure hospitalization was reduced

13  by 35 percent.  And the composite of heart failure

14  hospitalization or CV death was reduced by 34

15  percent.

16       In addition, the established safety profile

17  of empagliflozin was confirmed.  Our fulfillment of

18  the prespecified statistical plan of the EMPA-REG

19  OUTCOME trial not only allowed us to demonstrate

20  cardiovascular safety, but also allowed us to

21  propose the following indication for empagliflozin.

22  In adult patients with type 2 diabetes mellitus and

1    established cardiovascular disease, empagliflozin

2    is indicated to reduce the incidence of

3    cardiovascular death since this was the component

4    that drove the success of the primary endpoint.

5            Let us now take a look at the design of the

6    EMPA-REG OUTCOME trial, followed by results in more

7    detail.  The EMPA-REG OUTCOME trial examined the

8    long-term effects of empagliflozin on

9    cardiovascular morbidity and mortality, as well as

10   general safety in patients with type 2 diabetes and

11   established cardiovascular disease.  The study was

12   run by a steering committee, including

13   representatives from academia and the sponsor.

14           Our blinded adjudication panel and the data

15   monitoring committee consisted of independent

16   medical and statistical experts.  In addition, CV

17   outcome analysis were independently validated by

18   statisticians at the University of Freiburg.

19   Membership of the independent study panels are

20   included on page 49 of our briefing book.

21           EMPA-REG OUTCOME is a randomized,

22   double-blind, placebo-controlled trial.

Empagliflozin, 10 and 25 milligram, once daily were tested. There were three arms, and patients were randomized on a 1 to 1 to 1 basis. This was an event-driven trial targeting at least 691 events, patients with an adjudicated primary outcome event. Study treatment was added to local standards of care for patients with type 2 diabetes and established cardiovascular disease.

Prespecified and adjudicated endpoints in this trial included the following: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, transient ischemic attacks, hospitalization for heart failure, hospitalization for heart failure or CV death, and all-cause mortality.

Of these, 3-point MACE, which is the composite of CV death, nonfatal MI and nonfatal stroke was our primary outcome. 4-point MACE, which includes hospitalization for unstable angina in addition to the components of 3-point MACE, was a key secondary outcome. The prespecified and FDA

1  approved statistical analysis plan was to compare

2  pooled empagliflozin groups with placebo.  Type 1

3  error was controlled by hierarchical testing.

4       First, we tested for non-inferiority for

5  3-point MACE.  If statistical significance was

6  achieved, non-inferiority for 4-point MACE was

7  tested.  If non-inferiority was established,

8  superiority for 3-point MACE was tested, and if

9  successful, superiority for 4-point MACE was

10  tested.  These confirmatory endpoints were tested

11  on an alpha level of 0.0249, allocating a

12  0.001 alpha for the interim data extraction.

13       This interim analysis was done to support

14  the original new drug application of empagliflozin

15  to the FDA in 2013.  The 1-sided alpha level of

16  0.0249 equates to a 2-sided alpha of 0.0498.

17  Throughout the presentation, we will be reporting

18  2-sided alpha, consistent with our publications.

19       Other endpoints were tested at a nominal

20  alpha level of 0.05.  Non-inferiority was to be

21  concluded if the 2-sided upper bound of

22  95.02 percent confidence interval was lower than

1       1.3.

2                Superiority was to be concluded if the upper

3       bound of the confidence interval was lower than

4       1.0.  Analysis of cardiovascular outcome were based

5       on Cox proportional hazard models.  This

6       prespecified model includes treatment, age, gender,

7       baseline categories of BMI, HbA1c, eGFR, and

8       geographical region.

9                Patients who did not have an event were

10      censored on the last day they were known to be free

11      outcome.  For cumulative incidence functions for

12      all cardiovascular outcome events, except for

13      all-cause mortality, we censored patients at risk

14      by correcting for the competing risk of mortality.

15               The primary analysis was conducted in

16      patients treated with at least one dose of study

17      drug.  We referred to this population as

18      intent-to-treat population hereafter.

19      Additionally, on-treatment and per protocol

20      analysis were conducted.  The three treatment

21      groups are shown in columns.

22               Discontinuation of study medication was 29

1  percent in the placebo group.  These rates were

2  lower in both empagliflozin groups, 24 and

3  23 percent.  Ninety-seven percent of patients

4  completed the study.  These are the patients who

5  had an event contributing to the primary outcome,

6  or were known to be event free at the end of the

7  trial.  Final vital status was available for more

8  than 99 percent of patients.  The median

9  observation time was 3.1 years.

10        EMPA-REG OUTCOME trial was a global effort,

11  conducted at 590 sites, from 42 countries.

12  Countries were grouped into region as shown on this

13  map.  The next few slides show baseline

14  characteristics of these patients.

15        Study groups were balanced.  Mean age was

16  63.  Approximately one-third were women.  Patients

17  from the United States, Canada, Australia, and New

18  Zealand were pooled together as a prespecified

19  region.  Twenty percent of the total population was

20  from this pooled region, and 90 percent of these

21  were recruited from the United States.

22        Approximately 72 percent of patients were

white; 350 patients, 5 percent of the overall

population, identified themselves as black or

African-American.  Around a fifth were Asian;

18 percent identified themselves as Hispanic or

Latino.

Ninety-nine percent of the population had

established cardiovascular disease.  Approximately

three-quarters had coronary artery disease and

almost half had a history of myocardial infarction.

About 23 percent had a history of stroke;

10 percent had investigator-reported history of

heart failure at baseline.

Baseline HbA1c was around 8 percent.  The

mean body mass index was just over 30.  Patients

were well-controlled for blood pressure and

cholesterol.  Patients with an eGFR less than 30 at

screening were excluded per protocol.

Consistent with clinical practice, metformin

was the most commonly used oral glucose-lowering

therapy.  Approximately half the patients were

treated with insulin at baseline.  Ninety-five

percent of the population was on anti-hypertensive

therapy with ACE, ARBs the most common, used in

about 80 percent.  Beta blockers and diuretics were

used by approximately 65 and 43 percent of the

patient population.

Within the class of diuretics, the use of

loop diuretics was also balanced.  Around 80

percent of patients were on lipid-lowering drugs at

baseline.  And around 90 percent of patients were

treated with anti-coagulants or anti-platelet

therapies.  In this population, with established

cardiovascular disease, therapies to address

CV risk were widely used.

We also largely succeeded in keeping

patients in the trial and on study medication.

Discontinuation rates for empagliflozin was lower

than that of placebo.  We ensured optimal

ascertainment of outcomes by following up patients

irrespective of drug discontinuation.  This is

evidenced by the greater than 99 percent obtainment

of vital status.  Furthermore, we implemented a

process to ensure 100 percent source document

verification.

1          Let us now look at changes in cardio

2     metabolic parameters over the course of the study.

3     In these analyses, all patients, including those

4     who discontinued study drug or initiated new

5     therapies, were included.  This followed the

6     intent-to-treat principle.

7          During the first 12 weeks, glucose-lowering

8     therapy was meant to be kept stable.  Thereafter,

9     investigators were encouraged to treat patients

10    according to local guidelines for HbA1c targets,

11    adding additional glucose-lowering therapy if

12    necessary.

13         HbA1c reduction during the first 12 weeks

14    was consistent with the reduction previously

15    observed in the empagliflozin clinical development

16    program.  While glycemic equipoise was the

17    objective in the trial, a modest difference between

18    active drug and placebo persisted throughout, as we

19    have seen with other cardiovascular outcome trials

20    in type 2 diabetes.

21         Some weight loss was observed early, and

22    these findings were largely persistent throughout

1    the trial.  Both systolic and diastolic blood

2    pressure showed reductions with empagliflozin.

3    Heart rate remained largely unchanged.  Small

4    increases were observed in LDL cholesterol with

5    empagliflozin.  HDL cholesterol also showed small

6    increases.

7         Dr. Uli Broedl, head of clinical development

8    metabolism at BI, will now take you through the

9    cardiovascular outcome data.

10            **Applicant Presentation – Uli Broedl**

11        DR. BROEDL:  Good morning.  My presentation

12   will cover outcome related to MACE, CV death, heart

13   failure, and all-cause mortality.  The following

14   figure shows the cumulative incidence of 3-point

15   MACE.  The red line represents patients on

16   empagliflozin and the grey line placebo.

17        The vertical axis displays the percentage of

18   patients with events.  The horizontal axis shows

19   the number of patients at risk at a given point in

20   time.  Incidence rates per 100 patient years are in

21   parentheses.  Next to these we have provided the

22   number of events accrued, as well as frequencies of

1    events.  We will use this scheme throughout our

2    presentation.

3         This slide also shows the hazard ratio with

4    95.02 percent confidence interval and p-value.

5    Empagliflozin reduced the primary endpoint by

6    14 percent.  The hazard ratio was 0.86.  The upper

7    bound of the confidence interval was 0.99 with a

8    p-value of 0.0382.  This figure displays patients

9    on the two doses of empagliflozin separately,

10   10 milligrams in purple and 25 milligrams in blue.

11   Hazard ratios were virtually identical, 0.85 and

12   0.86.

13        We also looked at additional predefined

14   analyses populations.  In the intent-to-treat

15   population, the hazard ratio is 0.86.  In the

16   on-treatment population, defined as patients with

17   events occurring up to 30 days after last intake of

18   trial medication, the hazard ratio is 0.87.  And in

19   the per-protocol population, the hazard ratio is

20   0.86.

21        We have drawn a vertical dashed red line to

22   indicate the hazard ratio in the intent-to-treat

1    population.  The hazard ratios were virtually

2    identical in the three analyses populations.  We

3    will follow this scheme throughout today's

4    presentation.

5           We analyzed prespecified subgroups according

6    to baseline characteristics, including age, sex,

7    race, ethnicity, HbA1c, BMI, and eGFR.  This forest

8    plot shows the overall hazard ratio with 95 percent

9    confidence intervals for the intent-to-treat

10    population in the first row.  The subgroups are

11    listed in rows below.

12           The magnitude of the treatment effect was

13    generally consistent across predefined subgroups,

14    although, for this composite endpoint, some

15    heterogeneity was observed.  But please note that

16    when subgroups have a small number of events, they

17    are subject to play of chance.

18           We also tested a number of subgroups based

19    on concomitant therapies at baseline.  We observed

20    no meaningful heterogeneity in subgroups defined by

21    the use of glucose-lowering therapies, such as

22    metformin and insulin, lipid lowering agents such

1　as statins or ezetimibe, and anti-hypertensive

2　therapies, including RAS blockers, beta blockers,

3　and diuretics.

4　　　Let us now look at the individual components

5　of 3-point MACE; cardiovascular death, non-fatal

6　myocardial infarction, and non-fatal stroke.  The

7　effect on the primary endpoint was driven by a

8　38 percent reduction in the risk of cardiovascular

9　death, with little effect on the atherosclerotic

10　endpoints of non-myocardial infarction and

11　non-fatal stroke.

12　　　Looking beyond 3-point MACE to 4-point MACE,

13　which includes hospitalization for unstable angina,

14　non-inferiority was also achieved.  Similarly, the

15　hazard ratio for coronary re-vascularization was

16　0.86, with the upper bound of the confidence

17　interval crossing unity.  Of note, the point

18　estimate for non-fatal stroke was numerically

19　larger than 1.

20　　　So we will now present more detailed

21　analyses.  The next slide shows the cumulative

22　incidence of all stroke, including fatal and

non-fatal stroke in the intent-to-treat population. The analysis includes all events irrespective of whether patients were on-treatment or not.

Here, the hazard ratio was 1.18 with confidence intervals crossing unity. The curves overlap during periods of the trial where we followed most of the patients and observed most of the events.

We repeated this analysis for all strokes that occurred up to 90 days after drug discontinuation. In this analysis, the hazard ratio comes closer to unity. We further analyzed recurrent stroke, fatal stroke, or transient ischemic attack. Recurrent strokes, although infrequent, were balanced between placebo and the two empagliflozin groups. While the hazard ratio for non-fatal stroke was numerically greater than 1, the hazard ratio for fatal stroke was 0.72.

Transient ischemic attacks share the same pathophysiology as stroke. While the hazard ratio for stroke was numerically greater than 1, we see the opposite picture for TIA. The hazard ratio for

1    this adjudicated outcome is 0.85.  And if we look

2    at all stroke-like events, including fatal stroke,

3    non-fatal stroke, and TIA, the hazard ratio is

4    1.05.

5    We also looked at changes in hematocrit or

6    blood pressure and stroke.  No associations were

7    observed between stroke and changes in hematocrit

8    or blood pressure.  No associations were observed

9    between the occurrence of volume depletion and

10    stroke either.  Data supporting these conclusions

11    are provided in our briefing book.

12    So far, we have looked at components of the

13    primary endpoint, which were not significant.  Now

14    we will look more closely at cardiovascular death,

15    which was the principle driver of the primary

16    outcome.

17    Overall, 309 cases of cardiovascular death

18    occurred.  Empagliflozin showed a 38 percent

19    reduction in the risk of cardiovascular death.  The

20    hazard ratio was 0.62.  The 95 percent confidence

21    interval was 0.49 to 0.77, with a highly

22    significant nominal p-value.  These effects are

1    evident early in the trial and were sustained until

2    the end.  Both doses of empagliflozin yielded

3    comparable results for cardiovascular death.

4    Hazard ratios were 0.65 for the 10-milligram dose,

5    and 0.59 for the 25-milligram dose.

6         We also compared intent-to-treat and

7    on-treatment populations, as we did for stroke.

8    The two hazard ratios in the intent-to-treat and

9    on-treatment populations were comparable at 0.62

10   and 0.59.

11        This figure shows subgroups that we have

12   previously looked at.  There is no meaningful

13   heterogeneity across these subgroups.  And the

14   picture is similar when we look at concomitant

15   therapies used at baseline.  We observed no

16   meaningful heterogeneity in the effect of

17   empagliflozin on cardiovascular death.

18        What are the modes of cardiovascular death

19   that contributed?  All deaths were adjudicated by a

20   central, blinded, independent adjudication

21   committee based on prespecified criteria that are

22   consistent with guidelines.  The committee

1    categorized deaths into cardiovascular death and

2    non-cardiovascular death.

3         Cardiovascular deaths were further

4    classified into fatal MI, fatal stroke, heart

5    failure death, and sudden death.  Cardiovascular

6    deaths with full documentation, but due to causes

7    other than those four categories, were classified

8    under other CV cause.  These other causes included

9    dysrhythmia, pulmonary embolism, or coronary

10    intervention.

11         In addition, there were deaths where the

12    amount of information available was not sufficient

13    for the adjudication committee to definitely assign

14    into one of these categories.  As prespecified, in

15    this population with established cardiovascular

16    disease, all deaths not attributed to

17    cardiovascular death or non-cardiovascular death

18    were presumed cardiovascular death.

19         The next figure shows a hazard ratio and

20    95 percent confidence interval for the various

21    types of cardiovascular death.  Empagliflozin

22    reduced the risk of cardiovascular death by

1    38 percent.  The hazard ratio is 0.62.  Essentially

2    all categories of CV death, fatal MI, fatal stroke,

3    heart failure death, sudden death, and presumed

4    cardiovascular death showed a favorable point

5    estimate.

6         The most frequent causes of cardiovascular

7    death were heart failure death, sudden death, and

8    presumed cardiovascular death.  These modes of

9    death are commonly observed in patients with heart

10   failure.

11        To better understand the category of

12   presumed cardiovascular death, we looked at the

13   investigator-reported adverse events leading to

14   death in these patients.  As one would expect in

15   this population with established cardiovascular

16   disease, these investigator reports were largely

17   consistent with cardiovascular death.  Importantly,

18   even if one excluded presumed cardiovascular death

19   in a sensitivity analysis, reduction in

20   cardiovascular death remained highly significant.

21        Empagliflozin reduced cardiovascular death,

22   excluding cases of presumed cardiovascular death,

1    by 41 percent.  The hazard ratio was 0.59 with an

2    upper bound of the 95 percent confidence interval

3    of 0.79 and a highly significant nominal p-value.

4            To conclude this section on MACE and

5    cardiovascular death, a 38 percent risk reduction

6    in cardiovascular death drove the reduction in MACE

7    with no significant change in the risk of

8    myocardial infarction or stroke.  There was some

9    heterogeneity for subgroups of 3-point MACE.  The

10   findings of cardiovascular death however, were

11   consistent across the two doses, analyses

12   populations, and subgroups.

13           Modes of cardiovascular death associated

14   with heart failure were most frequent.  Therefore,

15   let us now look at heart failure outcomes in our

16   trial.  Heart failure hospitalization was a

17   prespecified and adjudicated endpoint in this

18   trial.  A composite endpoint of heart failure

19   hospitalization or cardiovascular death was also

20   prespecified.  This is an endpoint that is commonly

21   used in heart failure trials.

22           Empagliflozin reduced the risk of

1    hospitalization for heart failure by 35 percent.

2    The hazard ratio is 0.65.  The 95 percent

3    confidence interval was 0.5 to 0.85, with a highly

4    significant nominal p-value.  The effect was

5    evident early and persisted throughout the trial.

6         This figure shows heart failure

7    hospitalization within the two doses of

8    empagliflozin.  Hazard ratios for the 10- and 25-

9    milligram doses are 0.62 and 0.68 respectively.

10   Results for both doses were comparable.  We also

11   compared the consistency across adjudicated

12   hospitalization for heart failure, investigator-

13   reported heart failure, and initiation of loop

14   diuretics, a commonly used surrogate for heart

15   failure.

16        For adjudicated heart failure

17   hospitalization, the hazard ratio is 0.65.  For

18   investigator-reported heart failure, 0.70.  And for

19   the initiation of loop diuretics, it is 0.62.  This

20   consistency provides internal validity for the

21   hospitalization for heart-failure endpoint.

22        Empagliflozin also reduced the composite of

1    hospitalization for heart failure or cardiovascular

2    death.  Virtually identical results were seen for

3    this composite endpoint.  The hazard ratio was

4    0.66.  The 95 percent confidence interval was 0.55

5    to 0.79, with a highly significant nominal p-value.

6    Ten percent of the EMPA-REG OUTCOME population had

7    investigator-reported heart failure at baseline.

8    For patients with or without history of heart

9    failure, hazard ratios are comparable.

10         A similar result is seen for cardiovascular

11   death, suggesting that empagliflozin may reduce

12   heart failure hospitalization and CV death in

13   patients with and without preexisting heart

14   failure.  Empagliflozin reduced cardiovascular

15   death largely by reducing the risk of deaths that

16   are common in patients with heart failure.

17         The drug also prevented heart failure

18   hospitalization in patients with established

19   atherosclerotic cardiovascular disease.  The

20   composite endpoint of heart failure hospitalization

21   and CV death was reduced by 34 percent.  Results

22   were consistent for both doses and across

1    subgroups.

2          When a drug reduces cardiovascular death, it

3    is important that this benefit is not

4    counterbalanced by an increase in

5    non-cardiovascular death.  In EMPA-REG OUTCOME

6    trial, all-cause mortality was therefore included

7    as a predefined endpoint.  In this trial, vital

8    status was available for more than 99 percent of

9    patients, making the ascertainment of this

10   important endpoint methodologically robust.

11         As shown in this Kaplan-Meier plot,

12   empagliflozin reduced all-cause mortality by

13   32 percent.  The hazard ratio was 0.68.  The

14   confidence interval was 0.57 to 0.82, with a highly

15   significant nominal p-value.

16         Virtually identical results were observed

17   for empagliflozin 10 and 25 milligrams.  Hazard

18   ratios were 0.70 and 0.67 respectively.  We saw

19   similar results when we looked at intent-to-treat

20   and on-treatment populations.  The hazard ratios

21   are 0.68 and 0.69 respectively.

22         We also analyzed the contribution of

1    cardiovascular death and non-cardiovascular death

2    to the reduction in all-cause mortality. For

3    cardiovascular death, the hazard ratio is 0.62.

4    For non-cardiovascular death, the hazard ratio was

5    0.84.

6         The reduction in cardiovascular death with

7    empagliflozin was enough to be translated into a

8    reduction in all-cause mortality by 32 percent.

9    Results were based on a large number of events, 463

10    cases of all-cause mortality, consistent across

11    doses, across analysis populations, and across

12    subgroups.

13         We have seen the benefits of empagliflozin

14    on cardiovascular outcomes. Now I will hand over

15    to Dr. Woerle to discuss safety results.

16    **Applicant Presentation – Hans-Juergen Woerle**

17         DR. WOERLE: The next few slides will depict

18    the number of adverse events and their frequency.

19    We will show data for placebo, empagliflozin, 10-

20    and 25-milligram groups. Both doses of

21    empagliflozin were well tolerated. The safety

22    profile was consistent with previous trials with

1 empagliflozin.

2 Adverse events were comparable across three

3 groups. Occurrence of any adverse events leading

4 to discontinuation and serious adverse events were

5 all balanced with numerically fewer patients having

6 these adverse events on empagliflozin.

7 Drug-related adverse events occurred more

8 frequently on empagliflozin.

9 In addition to general safety, we examined

10 safety topics of particular relevance to

11 empagliflozin or the class of SLGT-2 inhibitors.

12 As previously observed in our registration trials,

13 genital infections were increased in patients

14 treated with empagliflozin. This was the case both

15 in men and women.

16 Volume depletion and venothrombotic events

17 were balanced. Urinary tract infections were

18 balanced between placebo and empagliflozin for male

19 and female patients. Urosepsis was infrequent, but

20 numerically higher in the empagliflozin groups. On

21 the other hand, pyelonephritis was comparable with

22 numerically fewer events in patients treated with

1    empagliflozin.

2        Diabetic ketoacidosis is included as a

3    labeled adverse event for all SLGT-2 inhibitors.

4    In the EMPA-REG OUTCOME trial, diabetic

5    ketoacidosis cases were infrequent, 1, 3, and 1

6    case in placebo, empagliflozin 10-, and 25-

7    milligram.  There was no imbalance in bone

8    fracture.  Cases of cancer were balanced.  Hepatic

9    injuries was also balanced with numerically fewer

10   events on empagliflozin.

11       Similarly, the risk of decreased renal

12   function was not increased.  Further reassurance

13   can be drawn from analysis of the time to first

14   occurrence of decreased renal function.  In this

15   analysis, the risk of decreased renal function is

16   significantly lower on empagliflozin in comparison

17   to placebo.

18       Furthermore, we looked at eGFR over time.

19   Patients on empagliflozin showed an initial dip in

20   eGFR, consistent with our registration trials, that

21   lasted up to 52 weeks.  These previous observations

22   led to a concern that empagliflozin may cause a

1    decline in eGFR, which is reflected in our current

2    label.  However, this picture appears to be

3    different over the entire course of the study.

4         eGFR in the placebo group showed the

5    expected decline in renal function of approximately

6    2 milliliters per year.  In contrast, eGFR in

7    patients on empagliflozin remained largely

8    unchanged.  These data suggest that the initial

9    worsening of renal function is transient, and over

10   time empagliflozin appears to slow the

11   deterioration of renal function.  These data are

12   reminiscent of the effects we see with the

13   initiation of ACE inhibitors.

14        The figure shows baseline characteristics at

15   last eGFR value on-treatment.  Patients were

16   enrolled thereafter for a median of 34 days.  In

17   the placebo group, the eGFR remained largely

18   unchanged during this follow-up period.  However,

19   in both the empagliflozin groups, eGFR almost

20   returned to baseline.

21        In addition, our trial included the

22   prespecified renal endpoint, new or worsening of

1     nephropathy. The hazard ratio for this

2     prespecified composite outcome was 0.61.

3     Confidence interval was 0.53 to 0.70, with a

4     p-value of less than 0.0001. New onset

5     macroalbuminuria, doubling of serum creatinine, and

6     initiation of renal replacement, all clinically

7     relevant components, contributed to the results

8     with hazard ratios of 0.62, 0.56, and 0.45

9     respectively; 3 renal deaths occurred on

10     empagliflozin, 10-milligram, none on placebo or

11     empagliflozin, 25-milligram.

12        In this analysis, only the time to first

13     event was considered. Nevertheless, we assessed

14     the same endpoints for sustainable changes, and the

15     findings are largely consistent.

16        To conclude this section on safety, no new

17     safety signals were identified in the EMPA-REG

18     OUTCOME trial. The rates of volume depletion, bone

19     fractures, venothrombotic events, hepatic events,

20     hypoglycemia, cancer, and DKA were comparable

21     between empagliflozin and placebo. General

22     infections were increased with empagliflozin, as

1    known from our previous trials.

2    The data that we have just seen suggests

3    that empagliflozin has no adverse impact on renal

4    outcome.  Empagliflozin appears to slow the

5    progressive decline in renal function in peril to

6    its favorable effects on cardiovascular death and

7    heart failure hospitalization.

8    Now, interpretation of the safety and

9    efficacy need to be made in the context of quality

10   and data integrity.  It is important to note that

11   the EMPA-REG OUTCOME trial was designed and

12   executed according to the contemporary clinical

13   trial standards and are now analyzed according to

14   prespecified statistical analysis plan.

15   Our plans for a CV outcome trial for

16   empagliflozin were driven by the 2008 FDA

17   cardiovascular guidance.  The initial objective of

18   this trial was to demonstrate cardiovascular safety

19   to fulfill the guidance by meeting non-inferiority

20   margin at the time of the NDA submission in 2013.

21   In 2011, based on emergent science and regulatory

22   feedback, we decided to expand the trial.  This

1  expansion to 7,000 patients aimed to accrue at

2  least 691 events, providing adequate power to test

3  not only for non-inferiority but also for

4  superiority.

5      In this trial, we prespecified an interim

6  data extraction to support empagliflozin's original

7  new drug application.  It is important to note that

8  we performed the interim analysis after major

9  amendments to the protocol were made.  The only

10  amendment that followed the interim focused

11  primarily on adjudication of hepatic and cancer

12  events.

13      An independent firewalled team performed the

14  interim analysis and regulatory submission, and all

15  trial personnel, investigators, and our

16  participants, were kept blinded throughout the

17  trial.  Neither the sponsor nor any regulatory

18  authority published EMPA-REG OUTCOME interim

19  results.  No major protocol changes were

20  implemented after the interim analysis.

21      Finally, we performed sensitivity analysis

22  to assess any potential impact of this interim

1    analysis.  When you look at trial population

2    recruited before and after the interim analysis,

3    results are comparable and consistent with the

4    overall trial population.  The hazard ratios for

5    cardiovascular death were also virtually identical.

6    Similarly, there were no differences in all-cause

7    mortality finding between the populations of

8    patients recruited before and after the interim

9    analysis.

10          Central adjudication of endpoints is another

11   key principle of trial quality.  Adjudication

12   criteria for endpoints were predefined indicia and

13   are shared across our CV outcome trials in

14   diabetes.  Endpoint definitions were reviewed

15   regularly by adjudicators for changes in clinical

16   practice and guidelines.

17          Whenever changes were made to endpoint

18   definitions, we re-adjudicated all events to ensure

19   consistency.  Importantly, the definition of

20   cardiovascular death, including presumed CV death,

21   remained unchanged throughout the trial in our

22   adjudication charter.

1        Changes to the endpoint definitions before

2    or after the interim analysis did not affect the

3    outcome.  Only events adjudicated as outcome events

4    were included in the MACE endpoint.  Silent MIs

5    occur in patients with type 2 diabetes, but its

6    ascertainment is challenging.  In previous

7    cardiovascular outcome trials in diabetes, the

8    occurrence of silent MI has been included in some

9    trials but not in others.

10       When a trial prospectively includes silent

11    MI in the primary endpoint, a formal process of

12    confirmation is put in place.  Now, in the EMPA-REG

13    OUTCOME trial, we decided not to include silent MI

14    in the primary endpoint.  Therefore, we did not

15    implement procedures to confirm such events.

16       Let us now look at missingness, another

17    important aspect of trial quality.  More than

18    97 percent of patients completed the study and we

19    had vital status in more than 99 percent.  In the

20    most conservative sensitivity analysis, in which

21    all patients on empagliflozin with missing vital

22    status were assumed to have died from

1   cardiovascular cause while all patients on placebo

2   to be alive, empagliflozin significantly reduced

3   cardiovascular death by 25 percent.  Hazard ratio

4   0.75, upper bound of the confidence interval 0.93,

5   with a highly significant nominal p-value.

6        We did similar analysis for all-cause

7   mortality presuming all patients on empagliflozin

8   without vital status had died, and that all

9   patients on placebo with vital status were alive.

10   Even in this worst-case analysis, empagliflozin

11   significantly reduced all-cause mortality by

12   23 percent.  The strength of these data provides a

13   firm foundation to make a complete assessment of

14   risk and benefits.

15        Professor Zinman will now provide his

16   clinical perspective.

17        **Applicant Presentation – Bernard Zinman**

18        DR. ZINMAN:  Thank you.  Since

19   cardiovascular death, as you've seen, is the number

20   one cause of mortality in diabetes, the results of

21   the EMPA-REG OUTCOME trial become particularly

22   relevant for our patients.  We've come a long way

1    in the prevention of macrovascular events in

2    patients with diabetes.  In the 1990s, major trials

3    established the importance of statin therapy as a

4    foundation for cardiovascular risk prevention in

5    people with diabetes.  ACE inhibitors then became

6    part of the standard of care, with demonstrated

7    beneficial effects on both renal function and

8    cardiovascular outcomes.

9            Now we have seen the added value of

10   empagliflozin, which in our trial was added to

11   standard of care, including statins and ACE

12   inhibitors.  We can now offer our patients a new

13   therapy that further reduces cardiovascular death.

14           What have we learned this morning from the

15   EMPA-REG OUTCOME trial?  First, and perhaps most

16   importantly, we now have additional confidence with

17   respect to the long-term safety of empagliflozin.

18   Secondly, in the context of patient care, treating

19   a thousand patients with type 2 diabetes and

20   established cardiovascular disease for 3 years with

21   empagliflozin would prevent 27 deaths, the vast

22   majority of which would be cardiovascular deaths.

1   Clearly, these remarkable and clinically relevant

2   benefits exceed the known risks associated with

3   empagliflozin.

4       I will now hand the microphone back to

5   Dr. Woerle to close the presentation.

6   **Applicant Presentation – Hans-Juergen Woerle**

7       DR. WOERLE:  We would like to thank our

8   patients, our investigators, our coordinators, and

9   members of the steering committee, adjudication,

10  and data monitoring committees.  Without their

11  contribution this large multinational, long-term

12  outcome trial would not have been possible.  We are

13  proud of the work that we have done together and

14  look forward translating these CV mortality

15  benefits to patients.

16      We have with us today a number of renowned

17  clinical trialists with expertise across several

18  disciplines:  Richard Bernstein, neurologist,

19  stroke expert; Jared Butler, heart failure

20  cardiologist; James Januzzi, cardiologist and

21  member of the adjudication committee; Robert

22  Makuch, statistical expert; Marc Pfeffer,

1   cardiologist; Stuart Pocock, statistical expert and

2   senior advisor to our data monitoring committee;

3   Christoph Wanner, nephrologist; Bernie Zinman,

4   endocrinologist and our trial chairman.  Thank you.

5               **Clarifying Questions to Applicant**

6           DR. SMITH:  Thank you.

7           We now have time for some clarifying

8   questions from the committee.  And the focus here

9   is really on data clarification.  We'll have time

10  for discussion later.  I see a few hands up

11  already.  If you would particularly signal to

12  Commander Bonner, she will list your names and I'll

13  try to get to everyone in order.  Dr. Hiatt?

14          DR. HIATT:  Thank you for a most informative

15  presentation, and I also found the background

16  material to be quite accessible.  My primary

17  question at this stage is to help us understand how

18  you got from a MACE primary endpoint to a

19  cardiovascular-labeled indication.

20          The question I think will probably be to the

21  FDA later in the day, but specifically the trial

22  was designed as a safety trial; 3-point MACE was

1    the primary endpoint.  In the hierarchal testing,

2    an adjustment of alpha was based on testing for

3    non-inferiority to demonstrate cardiac safety, and

4    then to superiority.

5          I specifically noted in your materials and

6    in the FDA materials that there was no hierarchal

7    testing on components of the primary endpoint or

8    other secondary endpoints.  So I don't understand

9    how we're going from MACE and the totality of the

10   cardiovascular events to a component of MACE that

11   seems selected to maximize demonstrating the

12   benefit of the drug.  And I guess I'd like you to

13   help me understand where that strategy came from

14   and how you can defend it.

15         DR. WOERLE:  Okay.  Empagliflozin reduced

16   3-point MACE, the primary outcome, by 14 percent on

17   top of standard of care, independent of glycemic

18   control.  This was entirely driven by a 38 percent

19   reduction -- can I have slide 3 up

20   please -- reduction in cardiovascular death,

21   without significant effects on the atherosclerotic

22   endpoints, non-fatal MI, and non-fatal stroke.

1          Now there are medical and methodological

2     reasons to support the CV indication, and I have

3     with us Dr. Pocock, who will give his statistical

4     perspective on the finding and this, if we are

5     allowed, will take a few minutes.

6          DR. POCOCK:  All right, thanks very much.

7     Besides being a statistical expert, I sort of

8     specialize in critiquing evidence of cardiovascular

9     outcome trials in general.  So what I'd like to

10    give with my first slide please, the next slide, is

11    my take on the strength of evidence and why it

12    merits concentrating on cardiovascular death.

13         My next slide, please.  As you have already

14    seen, the overview of the primary endpoint findings

15    are shown on this slide, showing a 10.5 percent

16    primary endpoint rate on both doses of

17    empagliflozin combined versus 12.1 percent on

18    placebo, which gives you a primary endpoint p-value

19    of 0.04, statistical significance in the

20    conventional sense.

21         Now, I think with all primary endpoints,

22    they are a mixed bag, and therefore you'd like to

1  understand what's driving it, because from a

2  clinical patient point of view, that's what really

3  matters.  Where does the benefit really lie?

4       Well, you see on the rest of this slide,

5  broken down by the three components, cardiovascular

6  death, myocardial infarction, and stroke, you see

7  that it's really all driven by cardiovascular

8  death, 3.7 percent versus 5.9 percent, with an

9  astonishing p-value, which you don't see very

10  often, of 0.0003, whereas for myocardial infarction

11  and stroke, there was no suggestion either way of a

12  really firm benefit or harm.  So then therefore you

13  concentrate on the component where the action is,

14  because that's what matters to patients.

15       Let's move to the next slide, please.  Then

16  you look for a consistency across doses, and this

17  is confirmed very clearly on this slide.  You can

18  see both for the 10-milligram and the 25-milligram

19  doses, you see a cumulatively lower rate of

20  cardiovascular death over time, substantially below

21  the grey placebo curve.

22       Above you see the hazard ratios for the two

1    separate doses, and that's very convincing.  You

2    see hazard ratio of 0.65 for the lower dose,

3    10 milligrams, and 0.59 for the higher dose,

4    25 milligrams.  And you see the high level of

5    statistical significance is still there when you

6    split by dose, p of 0.0016 and p of 0.0001

7    respectively.

8        Before I go to the next slides, I'd just

9    like to say it's important to see a consistency

10   across subgroups -- those were slides 54 and 55, to

11   be precise, in the earlier presentation -- and

12   showed that across subgroups you saw a consistency

13   of benefit of empagliflozin versus placebo for

14   cardiovascular death.  That was subgroups by

15   baseline characteristics for the patients and also

16   subgroups by different baseline treatments that the

17   patients were on.  So consistency is important.

18       My next slide, please.  Then we come into

19   multiplicity considerations.  Where does

20   cardiovascular death sit alongside all the other

21   endpoints that we could have considered?  So there

22   were 10 prespecified adjudicated cardiovascular

1    outcomes.  So are we cherry-picking the one that's

2    most significant, and if we are, how do we correct

3    for that?

4         Well, that's where Bonferroni correction

5    comes in.  It's a traditional way of multiplying

6    any p-value you see by the number of endpoints that

7    you could have studied.  And you see the p-value

8    for cardiovascular death then goes up to 0.003, so

9    still very, very convincing.  Multiplicity issues

10   aren't really of concern.

11        If you want to be particularly fussy you

12   could say what about all the endpoints,

13   microvascular and others, that we could have looked

14   at, 42 in all?  Even applying Bonferroni correction

15   in that circumstance, we could still get a

16   corrected p-value of 0.0012.  So there remains

17   strong evidence of benefit after corrections for

18   multiplicity.

19        Can I go to my next slide, please?  Now,

20   when we come to interpreting a remarkable benefit,

21   there is in the back of one's mind, is it too good

22   to be true.  And therefore I'm going to use -- I'm

1       not a natural Bayesian.  I often argue against

2       Bayesians in other messier settings.  But I think

3       it's an appropriate methodology to look at how we

4       can integrate the evidence we have in the trial

5       with the prior skepticism people might have had

6       about not expecting a cardiovascular death benefit

7       for empagliflozin.

8            The first slide here of this Bayesian

9       approach shows the observed data.  You say on a

10      hazard ratio scale in green, we see the peak of

11      what we're inclined to believe from the data alone

12      is an observed benefit of 0.62, 38 percent

13      reduction in cardiovascular death.  But we accept

14      the uncertainty of that estimate given the

15      finiteness of any given trial.  But do remember,

16      we're dealing here with 309 cardiovascular deaths

17      in the whole trial, so that's a considerably larger

18      amount of data than one normally gets in

19      cardiovascular outcome trials.

20           Therefore you see the spread of evidence

21      around that, so the probabilistic interval could go

22      from a benefit as high as a hazard ratio of 0.49,

1  51 percent reduction.  On the other hand, the data

2  themselves say, well it might go down on a

3  95 percent probabilistic basis, down to a hazard

4  ratio of 0.77, i.e. 23 percent reduction.

5          Now, my next slide, please.  It's

6  interesting to say, how can we express prior

7  skepticism?  You can just vaguely say it's all too

8  good to be true, but let's try and be a bit more

9  quantitative than that and say prior belief, in the

10  red curve, could have been that we really didn't

11  think empagliflozin would do anything to

12  cardiovascular death.  We have an aura of pessimism

13  from previous trials of previous drugs in diabetes.

14          But we could say, well, you never know.  So

15  let's propose that it could be beneficial, but we

16  think that benefit is unlikely to be more than

17  25 percent.  Or it could even be harmful, up to a

18  33 percent harm.  We just don't know before we do

19  the trial.  So let's see.  How can we put that

20  prior skepticism alongside the observed data?

21          The next slide, please.  That's where Bayes'

22  theorem comes in, and you end up combining the

1    evidence with the prior skepticism to say what

2    should we believe now.  In that spirit of too good

3    to be true, the prior skepticism does shrink the

4    estimate somewhat.  So you end up now with a

5    posterior belief, the most likely result is that

6    there's a true 26 percent reduction.

7         I think the data were perhaps a little bit

8    lucky in contrast to our prior belief, but there's

9    still a very positive outcome.  And that now ranges

10   from a possible 38 percent benefit down to just an

11   11 percent benefit, but with a strong tight

12   posterior belief.  In other words here, the data

13   are so strong they overwhelm prior skepticism

14   preserving an underlying positive belief now.

15        Move to my conclusions, please, the last

16   slide.  In general, evidence from secondary

17   endpoints need cautious interpretation in any

18   trial.  But here, mortality is clearly of huge

19   importance, far more important than non-fatal

20   outcomes.  As Dr. Zinman has pointed out, it merits

21   really special attention.  It really needs

22   improvements to patients.

1          But cardiovascular death is actually the key

2     component of the primary endpoint, so it's just

3     helping one interpret the primary endpoint result

4     where the action really is, which is of course

5     cardiovascular death.  A p-value of 0.0003 for

6     cardiovascular death is overwhelming evidence of

7     benefit.  You don't see that sort of strength of

8     evidence very often.  And sometimes, we therefore

9     adopt the phrase, proof beyond reasonable doubt of

10    great clinical importance to future patients.

11         Adding in non-cardiovascular deaths

12    preserves that survival benefit.  You've seen data

13    on that already.  And therefore this cardiovascular

14    death evidence establishes a strong foundation for

15    benefit-risk assessment of empagliflozin.  Thanks

16    very much.

17         DR. HIATT:  Thank you, but it didn't answer

18    the question, but it did provide more really

19    interesting statistical analysis, which I

20    appreciate.  The question is not why you get to CV

21    death.  The question is how you get there.  So

22    typically in a cardiovascular outcome trial, you

1    prespecify the primary and then you don't look at

2    the secondaries or components until you

3    statistically hit the primary, which you did on

4    superiority.  But because it's a safety trial, you

5    focused on the appropriate kinds of hierarchal

6    testing, which all makes sense.

7         What doesn't make sense to me is how -- and

8    since you're asking us to ignore the

9    fatal/non-fatal MI, fatal/non-fatal stroke, the

10    other cardiovascular components are sort of put to

11    the side because there's one compelling finding.

12    And I understand why we're there, and obviously

13    that's a mortality benefit, which is incredibly

14    important.  I just don't understand how you got

15    there, because legitimately this trial wasn't

16    designed to test a component of the primary in the

17    way you're doing it.

18         DR. WOERLE:  Let's review briefly the

19    statistical hierarchy of testing, because you say

20    this is a safety trial.  We started off with this

21    trial as a safety trial, this is correct, and the

22    trial was powered to demonstrate safety to pass the

1    1.8 hurdle.  And through the conduct of the trial,

2    we changed the scope of the trial.  We enlarged the

3    trial and we fully powered the trial with more than

4    690 events to demonstrate safety and potentially

5    efficacy.

6         May I have slide 3 up, please?  This is the

7    hierarchal testing procedure we have prespecified

8    in our statistical analysis plan and protocol.

9    When we started the trial, already in 2010, it

10   foresaw testing for non-inferiority of 3-point MACE

11   followed by testing for non-inferiority for 4-point

12   MACE.

13        Now, here comes the important part.  Both of

14   that has been fulfilled.  However now, superiority

15   for 3-point MACE was tested.  So up to this stage

16   superiority for 3-point MACE, we were successful.

17   However, we did not reach superiority for 4-point

18   MACE.

19        Now, superiority for 3-point MACE has been

20   established.  We describe in our current indication

21   statement the most important finding of the trial,

22   which is this large finding on cardiovascular

1   mortality, overall mortality and CV mortality being

2   reduced remarkably in a remarkable high number of

3   events of more than 300 or 400 events, whereas the

4   atherosclerotic components have not contributed.

5        We are of the belief that our data

6   interpretation is best reflected in a descriptive

7   statement that, while it has reduced significantly

8   3-point MACE, the most relevant finding to be

9   described is the finding on cardiovascular

10   mortality.

11        DR. SMITH:  Thank you.  This has been very

12   helpful, but I do want to stress that as we go

13   forward I would like the sponsor to be as brief and

14   focused as you can in answers so we have time to

15   get around to all the questions here.  So it's

16   really useful information, but as a precedent going

17   forward, I'd like to be as focused and brief as we

18   can.  Dr. Konstam, you had a question.

19        DR. KONSTAM:  Yes.  Thanks very much.

20        If Dr. Pocock wouldn't go too far away.

21   Maybe I can do this.  I'd like to just park my

22   request, which is that I'd like to see the impact

1    of missing data on the primary MACE endpoint,

2    success.  That's the gateway to anything else we

3    get and I haven't seen an analysis of missing data

4    effect on that.

5         So if you could, hold that.  But I'd like to

6    ask Stuart to follow up on his comments because,

7    first of all, I want to just say you know as well

8    as anybody that there have been a number of

9    observations of what look like fairly substantial

10   mortality benefits out of secondary endpoints,

11   subgroup analyses, components of the endpoint.

12   We've seen those before and in every case that I'm

13   aware of, when we went on and did the definitive

14   trial on that endpoint as the primary, it didn't

15   hold up.

16        In light of that, I think the issue of the

17   p-value to me is really very important.  And as you

18   know, the agency generally requires two trials, and

19   one of the ways they get around that is to say,

20   maybe if the p-value is real small, it's sort of

21   like two trials.  So we have this small p-value in

22   this secondary endpoint that is not part of the

1     hierarchal testing.

2         I get the Bonferroni correction. I think

3     that the hierarchy that was set up is actually

4     about adjusting for multiplicity. I mean that's

5     what it's there for. It's prespecified. It's

6     agreed to. I think that you can have strength that

7     you know what those p-values mean.

8         Now you take this other p-value that was not

9     part of the hierarchy and you say I can adjust that

10     by Bonferroni correction, not prespecified. And I

11     just want you to say, how can we really trust that?

12     What is the mathematical meaning of that p-value?

13     Is it sufficient to drive the two-trial

14     requirement?

15         DR. POCOCK: Well, I think it's partly

16     mathematical or statistical and partly what matters

17     to patients. So I'm a trialist. I'm more than

18     just a statistician. I'm a trialist. I

19     collaborate all my life in cardiovascular outcome

20     trials.

21         So I think we need to take here what matters

22     to patients in the context of the statistical

1  evidence.  And we have success in a formal

2  statistical sense on 3-point MACE.  You try saying

3  to the patient, we have a benefit on 3-point MACE.

4  He's kind of losing interest.  His cardiovascular

5  death is the driver.

6       DR. HIATT:  I get all that.  I get all that,

7  but I'm challenging your view that you can know

8  what that p-value really is, even though it was not

9  part of the hierarchy and it's a post hoc

10  Bonferroni adjustment.  How confident are you that

11  you know what that real p-value is?

12       DR. POCOCK:  Well, a p-value of 0.00003

13  is --

14       DR. HIATT:  Is small.  Yes, I get it.

15       DR. POCOCK:  -- pretty staggering.  I threw

16  Bayes at it to try and say can prior skepticism

17  overcome that.  It is a component of the primary

18  endpoint, which I think is important, but it's the

19  driver of the primary endpoint.

20       I have, on many occasions, talked about

21  composite endpoints in general.  And when one looks

22  at composite endpoints, always I say, in general,

1     not just about this trial, look at the details.

2     What's the driver within the composite?  And pretty

3     obviously the driver is cardiovascular death.

4          So people can nitpick about type 1 errors at

5     anything left, but cardiovascular death is there.

6     I think it's the most staggering result we have

7     seen in cardiovascular outcome diabetes trials

8     probably ever.  And therefore to stay within the

9     strict hierarchy of 3-point MACE, 4-point MACE, I

10    think is missing the point about the, importantly,

11    strength of evidence for cardiovascular death, a

12    component of the 3-point MACE, and obviously deaths

13    are more important than non-fatal events as well.

14         DR. SMITH:  Thank you.  Dr. Proschan, you

15    had a clarifying question?

16         DR. PROSCHAN:  Yes.  On CQ90, you talked

17    about the fact that the amendments were made before

18    looking at any data.  So what made you think that

19    you were going to be able to show superiority

20    without looking at the data?  That increase to

21    7,000 -- why did that thought even cross your mind?

22         DR. WOERLE:  The last part of your sentence,

1    I didn't hear.

2          DR. PROSCHAN:  Pardon?

3          DR. WOERLE:  The last part of your sentence

4    I didn't hear.

5          DR. PROSCHAN:  Well, basically, what made

6    you think that you were going to be able to show

7    superiority if you didn't look at the data?

8          DR. WOERLE:  Three things; medical

9    considerations, effect on blood pressure, of which

10   we know is very important when it comes to outcome.

11   We knew that the drug has a diuretic effect.  We

12   knew it reduces glucose and it reduces body weight.

13   From earlier trials, we saw that all relevant

14   biomarkers are going in the right direction.

15         We already speculated in 2010 about a

16   potential beneficial effect in heart failure, which

17   is very important when it comes to mortality in

18   type 2 diabetic patients.  That's why we

19   prespecified the endpoint heart failure and

20   adjudicated the events.  All those considerations,

21   together with some also preclinical evidence, led

22   us to enter this journey to test here for

1    full-blown superiority.

2           DR. PROSCHAN:  But weren't all those things

3    that you just mentioned -- weren't they available

4    before the trial?  So what made you decide that you

5    needed to amend it?

6           DR. WOERLE:  See, the guidance came out in

7    2008.  At the time we put together this trial,

8    together with our phase 3 program, there was a

9    large amount of uncertainty, how to best address

10    this issue.  There were proposals that you could do

11    two trials.  One, you do pre-registration.  You

12    could do another one post-registration and try to

13    pool.  Or you do a small trial and you see if you

14    clear the 1.8 hurdle, and then you do another

15    trial.

16          We had some consultation also with the FDA

17    as part of our end of phase 2 meeting.  Together

18    with statistical consideration, we said the best

19    approach is to go with one large trial, which

20    allows you to test for non-inferiority and

21    superiority.  And this thinking process took some

22    time until we took the decision.

1      DR. SMITH:  Dr. Cooke, you had a question?

2      DR. COOKE:  With regard to the

3  cardiovascular outcomes, including 3-point MACE and

4  the others, when you look at the efficacy of the

5  two different doses, it seems like they basically

6  overlap.  So I'm curious, your interpretation of

7  why there's a lack of a dose-response effect.

8      DR. WOERLE:  When we knew from early trials

9  in phase 2b -- remember, when we designed this

10  trial at a point we had no information on larger

11  scale trials, but we knew from our phase 2b trials

12  that there is a small dose response in terms of

13  HbA1c and very subtle also in terms of blood

14  pressure lowering and BMI.

15      We knew from earlier trials in diabetes that

16  the small differences in glycemic control, which we

17  most likely will see in phase 3, will not

18  contribute to hard outcome, because this takes, if

19  any, 10 years or longer to establish.  So our

20  underlying assumption was that most likely we will

21  see very similar results with, if any, very small

22  dose response effects in terms of hard outcome.

1    And that's exactly what we saw.

2         But what is remarkable?  I wanted to make

3    that point about the assurance of the data, that we

4    see this consistency with two doses.  And even

5    though it's not entirely proper, but you almost

6    could see this as two studies in one, with this

7    remarkable consistency on CV death.

8         DR. SMITH:  So I have a question.  And what

9    I'm looking for is some more clarification on the

10   non-assessable death category being assigned to

11   presumed cardiovascular death.  I still don't fully

12   understand.  What I'm looking for is to understand

13   what you actually did and some of the specifics of

14   that.  Because I understand the words, but I

15   actually don't have a good clinical understanding

16   of what was done and what those patients were.

17        DR. WOERLE:  Cases of CV death that could

18   not be attributed to CV death or non-CV death were

19   prespecified in our adjudication charter as

20   presumed CV death.  Now, fortunately, we have today

21   Dr. Januzzi with us, who was part of the

22   adjudication panel who adjudicated all those

1    events, who is best equipped to address your

2    question.

3         DR. JANUZZI:  Good morning, everyone.  It's

4    a pleasure to represent the clinical endpoints

5    adjudication committee.  We're an independent group

6    of cardiovascular specialists and clinical

7    trialists that review the cases through the several

8    years of the study.  And specifically, what I'd

9    like to do is answer the question that Mr. Chairman

10   posed, but address on a methodological level this

11   question of the higher number of presumed CV death

12   events.

13        The first point, as any clinical trialist

14   will know and people that have performed clinical

15   endpoints adjudication, the heart and soul of the

16   CEC is the charter by which we judge cases.  We

17   review cases from the beginning to the end of the

18   trial using the charter as our gold standard.

19        So in order to provide high level and

20   consistent high quality data, it's necessary for

21   the CEC to follow specific definitions in evidence

22   requirements to meet the definition of

1    cardiovascular death, or non-cardiovascular death

2    as prespecified in the adjudication charter.

3    Stated in a more simple way, if patients were

4    submitted for event review that did not meet

5    specifically the expectations outlined in the

6    charter, by definition, they were presumed CV death

7    because of the lack of ability to assess.

8         The point here is it's done to ensure

9    consistent evidence-based and reproducible work

10   from beginning to end of trial out of the

11   adjudication committee.  So therefore, the high

12   number of presumed CV death, in the opinion of the

13   reviewers, reflects the fact that we adhere very

14   carefully to the definitions set forth in the

15   charter for meeting CV death.

16        Now, Mr. Chairman, to answer your specific

17   question, this was a broad range of possible

18   scenarios, as you probably know through your

19   review.  In many trials, for example, patients

20   found dead in bed would be classified in some

21   studies as sudden cardiac death, whereas in the

22   EMPA-REG OUTCOME study, if we lacked the specific

1    variables to judge sudden cardiac death, we would

2    be compelled to call it presumed CV death.  So

3    that's just one example of how those numbers might

4    be affected somewhat through our processes.

5         DR. SMITH:  Okay, I think I'm getting more

6    clear about it, but I see -- Dr. De Lemos, yes?

7         DR. DE LEMOS:  Pull up CO-57.

8         DR. WOERLE:  Slide up, please.

9         DR. DE LEMOS:  Just to clarify,

10    three-quarters of the cardiovascular deaths in this

11    trial were either sudden death or presumed CV

12    death.  And so that's really the issue if we're

13    going for a CV death claim here.  And the

14    question -- in the charter, the individuals with

15    sudden death include a last category on page 124 of

16    your briefing document, where the last category of

17    sudden death is presumed CV death.

18         Now, is this category at the bottom that

19    category?  Or in fact some of the sudden death is

20    actually unwitnessed so that the proportion of

21    individuals in whom we really don't know how they

22    died is actually larger?  Does that make sense, my

1    question?

2            So the sudden death definition in the

3    charter includes both witnessed sudden death and

4    unwitnessed death.  And the question is, is that

5    bottom category the unwitnessed sudden death or are

6    many of those sudden deaths actually unwitnessed?

7            DR. JANUZZI:  That's a good question, James.

8    So basically, in order to be termed sudden death,

9    they had to meet specific charter definitions.

10   Therefore, in the presumed CV death, there were

11   patients that were found dead in bed, is the term

12   that's used, who, given their background

13   cardiovascular risk.

14           These patients were enrolled in a

15   cardiovascular safety trial.  The mode of death in

16   many trials would have been called sudden death.

17   But in this study, because they did not meet the

18   charter definitions, we called them presumed CV

19   death.  Maybe I'm not being clear.  To be simple --

20           DR. DE LEMOS:  Well, there's a bullet.  The

21   question is how many of the sudden -- there are

22   five bullets under the sudden death definition.

1    Four of them require some witnessed event, and the

2    fifth says -- the fifth bullet under sudden death

3    reads, "Unwitnessed death," and there's no

4    conclusive evidence of another non-cardiac cause of

5    death.

6         The question is, did you pull that group out

7    as presumed CV death?  Or in fact are the sudden

8    deaths mostly unwitnessed as well, in which case

9    the conclusion is that we basically don't know why

10   the large majority of these people died, which is

11   understandable?  It's hard to figure out why people

12   die in an outpatient trial, but if it's a CV death

13   claim, that's a different question.

14        DR. BROEDL:  Uli Broedl, Medicine.  To

15   answer your question, indeed in addition to the

16   requirement of witnessed death, there was one

17   bullet point, as depicted in our briefing book,

18   that refers to an unwitnessed death.  But it also

19   says that the patient should have been seen alive

20   within the last seven days.

21        So in essence, if someone has not been seen

22   for more than a week or so and then was found dead

1    in bed or if, for instance, at the end of the day

2    we have only very limited information what happened

3    to this patient, this patient could then either be

4    categorized, if seen within the last seven days, as

5    sudden death.

6         Or if nothing was available and the patient

7    has been seen for quite some time or limited

8    information, or only at the end of the day a death

9    certificate was available, those patients would

10    have been categorized according to the prespecified

11    charter as presumed CV death.

12         DR. DE LEMOS:  Would it be possible at the

13    break to pull them out?  I think when we're

14    thinking about an indication in a single trial to

15    meet a definition of CV death, it's important to

16    see what the impact of these presumed deaths and

17    these unwitnessed deaths are on the strength of the

18    association for a single trial for CV death, I

19    think.  And that goes to Marv's point, I think

20    about --

21         DR. BROEDL:  Then maybe Dr. Januzzi can

22    comment on this.  But what has been reported on the

1    CEC voting form, at the end of the day, is CV death

2    and then the type of CV death, but not the reason

3    why presumed CV death versus sudden death was

4    chosen.  So we cannot just break down the five

5    bullet points.

6         But what we can do to give you some

7    reassurance is review slide 1, please again, which

8    is the sensitivity of the cardiovascular analysis

9    that I have presented earlier today.  Given the

10   uncertainty around presumed CV death, we conducted

11   this sensitivity analysis where we excluded

12   presumed CV death, 124 cases.  And the results for

13   empagliflozin on CV death remained significant,

14   virtually identical.

15        DR. SMITH:  So if I understood, you're not

16   able to produce the requested breakdown in

17   data -- did I understand that -- for later today,

18   as Dr. De Lemos was requesting?

19        DR. BROEDL:  That is correct.

20        DR. SMITH:  All right.  I think we should

21   move on now.  We've got just a few more minutes

22   here before the break.  Dr. Good had a question.

1          DR. GOOD:  Thank you.  As a neurologist, I

2     do have a question about the important secondary

3     outcome measure of non-fatal stroke.  Of course, as

4     you pointed out, the HR is higher in the treatment

5     group compared to placebo, although it's not

6     statistically significant, I understand that.  So,

7     you noted, when you added TIA, that the HR

8     approached 1.

9          So a comment -- the diagnosis of TIA has

10    some clinical noise in it.  Some things that are

11    thought to be TIAs are not TIAs, and it might

12    falsely suggest that it isn't as close to 1 as you

13    suggest.

14         The other thing I'd be interested in is that

15    I'd be interested in the number of disabling

16    strokes, which is quite important to patients, and

17    how you determine the disability.  You may want to

18    talk about this, this afternoon.

19         The final thing I want to comment on is the

20    disparity between stroke incidence among different

21    regions.  In fact, there's some suggestion that the

22    incidence in Europe was much, much higher than

1    other regions, and that puzzles me.  It suggests

2    there's a variability perhaps in diagnosis in

3    different regions, and Latin America is very low.

4    So I'd just like you to comment on that and it

5    raises some question in my mind about the accuracy

6    of diagnosis across the regions.

7            DR. BROEDL:  First we have to say, this

8    trial was set up as a cardiovascular outcome trial.

9    We did not set it up as a stroke trial.  So there

10   is some certain limitation on the degree of

11   information we have from this trial.

12           From our point of view, the most important

13   hazard ratio is actually fatal and non-fatal stroke

14   together, because that should go along with each

15   other.  And there, the hazard ratio is 1.18, with

16   largely overlapping confidence interval, indicating

17   a non-significant finding.

18           We have a team here of Sven Koehler and a

19   stroke expert who reviewed extensively the data.

20   And I would ask Richard Bernstein, who is a stroke

21   expert, to give his assessment on when he looked at

22   the stroke data, in particular on disabling stroke

1    and also the regional question.

2         DR. SMITH:  Again, what I'm going to ask for

3    is to as specifically and briefly as possible

4    answer the question that Dr. Good has raised,

5    rather than just give us some more background on

6    this.

7         DR. BERNSTEIN:  Thank you.  My name is

8    Richard Bernstein.  I'm a stroke neurologist and

9    stroke clinical trialist at Northwestern

10   University.  Thank you, Dr. Good, for your

11   question.  Let me talk first about the stroke

12   severity issue relating to fatal and non-fatal.

13   Slide 2 up, please.

14        When we reviewed stroke in some detail, when

15   I did with the team, we wanted to look at the range

16   of severity of stroke endpoints because of this

17   1.18 hazard ratio.  And if this finding were a real

18   finding, for example, I would have expected to see

19   an increase across the range of severity from

20   fatal, non-fatal, non-disabling, and TIA, which are

21   all really the same disease.

22        In fact, if you look at this forest plot,

1    what is see is the point estimate bouncing back and

2    forth across unity, so that there are fewer fatal

3    strokes and disabling strokes, a few more non-fatal

4    strokes, fewer TIAs.  And if you put stroke plus

5    TIA together as a total cerebral vascular event

6    count, we're at about unity.  So to me, this

7    oscillation back and forth suggests that it's all

8    sort of a random finding.

9         Regarding region, if we could get the slide

10   up by different regions, yes, here we are.  Slide

11   2, please.  Thank you.  So looking at stroke by

12   region, what's most striking to me is what is

13   likely anomalously low incidence of stroke in the

14   placebo group, which as a clinical trialist is the

15   thing you never really want to see.  But we were

16   unable, in going through all of the risk factors

17   and data in detail, to find any explanation.  And

18   so my conclusion is this is a chance finding.

19        DR. SMITH:  Okay, Dr. Neaton, you had a

20   question?

21        DR. NEATON:  I did.  Thank you.  So

22   actually, I had a question that will ultimately

1   lead to the same one Dr. Konstam had.  So you had

2   an extreme result for cardiovascular mortality, but

3   the component for which it's part, 3-point MACE,

4   the p-value is more borderline.  And there's also

5   more unknown information about those events than

6   for mortality, which makes sense.

7        So two questions.  One, precisely, I could

8   not determine how you did the censoring when you

9   did the 3-point MACE because there were deaths,

10  obviously, which must have occurred after you

11  became unknown about the non-fatal status, for

12  example, and how those were handled.  And also what

13  other sensitivity analyses were done around that

14  3-point MACE outcome that kind of prompts us, if

15  you will, to think very carefully about the

16  contributing components?

17       DR. WOERLE:  We counted.  This was a time to

18  first event analysis, so patient could have had a

19  stroke, time to first event.

20       DR. NEATON:  No, I understand that, but I'm

21  particularly interested in understanding precisely

22  when you censored follow-up for people when they

1 had an unknown event status because the unknown

2 event status could have happened earlier for

3 non-fatal events than fatal events.

4 　　　DR. WOERLE:  I see.

5 　　　DR. NEATON:  So presumably a person could

6 have died from cardiovascular disease after you

7 lost track of them for non-fatal MI and stroke.

8 　　　DR. WOERLE:  Our project statistician is

9 best equipped to answer this question, Stefan

10 Hantel, may I ask you?

11 　　　DR. HANTEL:  Stefan Hantel, biostatistics.

12 When we looked at MACE 3, we censored the patient

13 as presented in the presentation at last time when

14 we were aware that the patient was event free.

15 This means vital status and knowing that the

16 patient is alive at study end was not sufficient.

17 Therefore, we have only 97 percent of patients

18 followed up for MACE 3 at the end of the trial, but

19 99 percent for vital status.

20 　　　So the difference is that we censored

21 patients with a positive vital finding in the sense

22 that the patient was still alive at the last time

1   we were aware that the patient was event free for

2   non-fatal stroke, non-fatal myocardial infarction.

3         DR. NEATON:  Presumably a person could have

4   died from cardiovascular disease after that time

5   point and they would have been excluded from the

6   analysis?

7         DR. HANTEL:  These patients were included

8   because we tried to capture the event.  So you are

9   right.  In this patient, it can happen that we

10   missed a non-fatal event.  But if you focused on --

11         DR. NEATON:  More of my question is, what

12   happens if you've lost track of their non-fatal

13   endpoint status and then later on, you determine

14   that they've died, say, from cardiovascular

15   disease?  Is that event counted?

16         DR. HANTEL:  Yes.

17         DR. NEATON:  It is counted?

18         DR. HANTEL:  Yes.

19         DR. NEATON:  So what sensitivity analyses

20   have you done around that censoring mechanism, and

21   more generally the missing non-fatal endpoint, to

22   kind of convince us that 0.038 is really robust?

1          DR. HANTEL:  We had prespecified sensitivity

2    analysis focusing on events happening up to 30 days

3    after treatment stop.  This was presented earlier

4    today.

5          DR. NEATON:  But we're interested in the

6    missing data.  You had 144 people, for example,

7    with unknown non-fatal endpoint status for MACE 3.

8          DR. HANTEL:  What we did for MACE 3, when we

9    assume, looking at vital status, patients are that

10   in EMPA and alive in placebo.  The hazard ratio is

11   almost unchanged.  When we went through this

12   analysis for MACE 3, assuming that those patients

13   we didn't follow up to the end, we would lose

14   significance for superiority but still maintain

15   non-inferiority.

16         DR. NEATON:  That's a very extreme kind of

17   sensitivity analysis and so I accept that that's

18   what you would find, but have you done any kind of

19   analyses to understand the reasons for missingness

20   that would give us kind of something that might be

21   closer to the truth?

22         DR. HANTEL:  What we did not perform is like

1    multiple implementation to address missingness.

2    What we can show you is time to censoring for

3    MACE 3.  Slide 2 up, please.  And here we see that

4    the time to censoring is not really different

5    between empagliflozin and placebo.

6         DR. NEATON:  I only see one line --

7         (Laughter.)

8         DR. HANTEL:  I'm close enough, so there are

9    some small differences, but it's virtually

10   identical.

11        (Laughter.)

12        DR. NEATON:  We'll come back later and talk

13   to you about your next presentation about the

14   censoring.  Thanks.

15        DR. WOERLE:  Yes.  It tells you about the

16   accuracy of our statisticians.

17        (Laughter.)

18        DR. SMITH:  We need to take a break.  We're

19   going to take about a 15-minute break.  I'm going

20   to start just a little bit before 10:30, and we'll

21   return to those panel members who have questions

22   that we didn't get to.  We'll get to those later

1   today.

2          Panel members, please remember there should

3   be no discussion of the meeting topic during the

4   break among yourselves or with any member of the

5   audience.  So we'll start about 28 past the hour

6   here.

7          (Whereupon, at 10:14 a.m., a recess was

8   taken.)

9          DR. SMITH:  I would like people to start

10  taking your seats.  We're going to start in just

11  another minute or so here.  So we'll now proceed

12  with the FDA presentations, and we will come back

13  to more clarifying questions later on today.

14          **FDA Presentation – Andreea Lungu**

15          DR. LUNGU:  Good morning.  My name is

16  Andreea Lungu, and I'm a clinical reviewer in the

17  Division of Metabolism and Endocrinology Products.

18  On behalf of the review team, I would like to thank

19  the committee for being here today.

20          Today, I will be presenting the FDA's review

21  of the findings from the EMPA-REG OUTCOME study.  I

22  will refer to this study as the EMPA-REG study

1    throughout my presentation.  I will --

2          DR. SMITH:  Could we have the volume up just

3    a little bit?

4          DR. LUNGU:  I will begin by briefly

5    reviewing the regulatory history for this trial,

6    which is complex.  I will follow with a description

7    of the EMPA-REG OUTCOME trial, including the

8    objective, design, trial conduct, and study

9    population.  Dr. Jennifer Clark will then present

10   the FDA's statistical assessment.

11          Following her presentation, I will discuss

12   the factors affecting the interpretation of the

13   primary endpoint, selected exploratory endpoints,

14   followed by some of the non-cardiovascular safety

15   findings.  I will then conclude with a summary of

16   the FDA presentation.

17          The EMPA-REG OUTCOME trial was conducted to

18   address the 2008 guidance for industry on

19   evaluation of cardiovascular risk for new

20   anti-diabetic drugs, and was primarily designed to

21   address a safety question.  As a result, the trial

22   design may differ from trials conducted to address

1    an efficacy question.

2         As a reminder, the guidance recommends that

3    applicants exclude 80 percent excess ischemic

4    cardiovascular risk pre-approval, and 30 percent

5    excess ischemic cardiovascular risk post-approval.

6    This can be achieved through a meta-analysis or a

7    dedicated trial.  I will now discuss how the

8    EMPA-REG study was utilized to address this

9    guidance.

10        The role of the EMPA-REG study in the

11   cardiovascular risk assessment evolved over time,

12   and changes to the trial design occurred while the

13   trial was ongoing.  These changes, to some extent,

14   reflected changes in the applicant's strategy to

15   address various aspects of the guidance, and were

16   in part informed by advice received from the FDA.

17        The initial proposed cardiovascular risk

18   assessment is shown here.  The EMPA-REG study is

19   shown in red and was to provide cardiovascular

20   events for the purpose of evaluating the

21   pre-approval cardiovascular risk margin only.

22   There were three planned looks to exclude the

1    1.8 risk margin, denoted by the three arrows.  The

2    first was to occur at completion of phase 3

3    diabetes trials.  The second was to occur when

4    60 events had accrued, and the last after accrual

5    of 152 events.

6         The role of the EMPA-REG study in the

7    assessment of the post-approval cardiovascular risk

8    margin was unclear.  The agency communicated that

9    this proposal lacked clarity, did not sufficiently

10   control for type 1 error, and was not powered to

11   address the 1.3 risk margin.  The agency asked that

12   these issues be addressed before agreeing to the

13   plan.

14        The second proposal for the cardiovascular

15   risk assessment is shown here.  The EMPA-REG study

16   is again shown in red.  In this proposal, the

17   EMPA-REG study was to provide events for the

18   purpose of evaluating both the pre-approval and

19   post-approval cardiovascular risk margins.

20        The applicant proposed to evaluate the 1.8

21   cardiovascular risk margin using a meta-analytic

22   approach and to perform the first analysis when 118

1    MACE-plus events had accrued.  The applicant

2    proposed to then initiate a second cardiovascular

3    outcomes trial, shown in green, which would be

4    combined with the EMPA-REG study to evaluate the

5    1.3 cardiovascular risk margin using a

6    meta-analytic approach when 711 MACE-plus events

7    had accrued.

8         The applicant had plans to test both

9    noninferiority and superiority hypotheses after

10   accruing all 711 events.  The FDA commented that

11   increasing enrollment in the EMPA-REG test both

12   non-inferiority and superiority study would be more

13   efficient than initiating a second study for the

14   purpose of excluding the 1.3 cardiovascular risk

15   margin.

16        The FDA also expressed reservations with the

17   applicant's plan to use a meta-analytic approach to

18   test for superiority for the purpose of obtaining a

19   cardiovascular risk reduction claim.  The FDA

20   recommended that the applicant consider using a

21   dedicated outcomes trial if their intent was indeed

22   to pursue a potential cardiovascular risk reduction

1  claim.

2      The final cardiovascular risk assessment

3  plan is shown here.  The plan to exclude the 1.8

4  risk margin remained the same.  The plan no longer

5  sought to rely on a second cardiovascular outcomes

6  trial to accrue sufficient number of events, but

7  added an additional 3,000 patients to the ongoing

8  EMPA-REG study instead.  Changes to the EMPA-REG

9  study protocol were made to reflect this change in

10  strategy and submitted with the final

11  cardiovascular risk assessment plan.  The FDA

12  agreed with this plan.

13      With this final plan, the protocol was

14  changed and the trial size was adequate from this

15  point onward to independently exclude the 1.3 risk

16  margin for MACE.  The protocol specified that the

17  trial would stop once 691 MACE events accrued.  The

18  protocol also specified that the planned interim

19  analysis would occur after 118 events had accrued.

20      The plan for the interim appropriately

21  adjusted the type 1 error to account for this

22  interim look.  Superiority testing was allowed, and

1    was to be conducted only after the 1.3 risk margin

2    was excluded for both MACE and MACE-plus.

3            The empagliflozin new drug application was

4    submitted in March 2013.  The database for the

5    EMPA-REG OUTCOME study interim analysis supporting

6    the pre-marketing cardiovascular risk assessment

7    had been locked on August 21, 2012.  The analysis

8    for the pre-marketing cardiovascular risk margin

9    was based on a total of 196 MACE events, with the

10   majority of these events being contributed by the

11   EMPA-REG study.

12           Interim data from the EMPA-REG study was

13   used to test both the 1.8 and 1.3 risk margins at

14   that time.  To give you an idea of the ongoing

15   trial, approximately 5,000 patients had been

16   randomized into the EMPA-REG study at the date of

17   the database lock.

18           Finally, to support regulatory filing of the

19   application in the U.S. and worldwide, some level

20   of unblinding at the applicant level occurred.

21   Indeed, approximately 230 individuals were given

22   access to patient-level data and interim results

1    for the ongoing trial.  The unblinded individuals

2    were required to sign a confidentiality agreement

3    stating that the results would be kept

4    confidential.

5        The results of the prespecified

6    pre-marketing cardiovascular risk analysis revealed

7    no signal of increased cardiovascular risk

8    associated with the use of empagliflozin.  The

9    hazard ratio for 1.8 and for the prespecified

10   interim analysis for 1.3 are shown here.

11       Empagliflozin was approved in August 2014.

12   At the time of approval, the FDA required that the

13   applicant continue evaluating the cardiovascular

14   risk associated with empagliflozin use by issuing a

15   postmarketing requirement.

16       The requirement specified that the EMPA-REG

17   study alone be used to evaluate the postmarketing

18   risk margin, and that the assessment be based on

19   3-point MACE.  Adverse events of interest,

20   unrelated to cardiovascular risk, were to be

21   collected as part of that requirement.

22       Having covered the regulatory history, I

1     want to now spend some time reviewing the study

2     design and study conduct.  There were some general

3     features of the design that did not change over the

4     course of the study, and these are illustrated

5     here.

6           The study was always a randomized,

7     double-blind, placebo-controlled trial.  The study

8     population evaluated in the study were adults with

9     type 2 diabetes who were also at high risk for

10    atherosclerotic cardiovascular disease.

11          The duration of the study was always to be

12    event driven.  Subjects were randomly assigned to 2

13    doses of empagliflozin or placebo in a 1 to 1 to 1

14    fashion.  The investigational drug or placebo were

15    added to local standard-of-care drugs for both

16    diabetes and atherosclerotic cardiovascular

17    disease.

18          Therapies for diabetes and atherosclerotic

19    cardiovascular disease were to be adjusted

20    throughout the trial by treating physicians to

21    achieve therapeutic targets set by local

22    professional guidelines.  These instructions were

1    expected to result in minimal differences in

2    glycemic control and cardiovascular risk factors

3    susceptible to confining interpretability of the

4    final study results.

5         The primary objective of the study was to

6    evaluate the ischemic cardiovascular risk of

7    empagliflozin, and the primary endpoint variable

8    was always the time to a first major adverse

9    cardiovascular event consisting of a 3 part

10   composite comprised of cardiovascular death,

11   non-fatal myocardial infarction, and non-fatal

12   stroke.

13        Key participants involved in study conduct

14   and operation also did not change.  The applicant

15   was responsible for the conduct of the trial,

16   communication between investigators and various

17   committees and regulatory bodies, analyzing the

18   interim and final results, and reporting these

19   results to the various worldwide regulatory

20   agencies.

21        The steering committee provided scientific

22   leadership for the design and conduct of the study.

1     An independent data monitoring committee was

2     established to monitor the progress, safety, and

3     efficacy of the empagliflozin phase 3 clinical

4     trials, including the EMPA-REG.

5          The clinical event committee was responsible

6     for central blinded adjudication of all major

7     adverse cardiovascular events.  This committee was

8     also to adjudicate MACE events for another

9     anti-diabetic program.

10          Finally, the general process for event

11    adjudication did not change drastically over the

12    course of the study.  All fatal events and any

13    events suspected of stroke, transient ischemic

14    attack, myocardial ischemia, hospitalization for

15    unstable angina or heart failure, stent thrombosis,

16    and revascularization procedures were to be

17    referred for adjudication.  The adjudication

18    process, briefly outlined on this slide, was a

19    standard adjudication process for outcomes trials.

20          While the general features of the trial did

21    not change drastically, there were some important

22    changes made over the course of the trial to the

1    clinical trial protocol, the CEC charter, and

2    statistical analysis plan that I will now discuss.

3    To frame that discussion, it may be helpful to

4    orient yourselves with some of the major milestones

5    of the trial, which are shown in the figure.

6         The date of first consent occurred in July

7    2010, and the first patient was randomized in

8    Canada on September 15, 2010.  At this point, the

9    FDA had not seen the protocol.  The date for

10   interim data cutoff was June 22, 2012, and the date

11   of interim database lock was August 2012.  The last

12   visit for the last subject occurred April 13, 2015,

13   and the date of final database lock occurred on

14   June 22, 2015.

15        I will use this timeline as a frame of

16   reference to describe other changes.  I will

17   discuss some of the major changes, starting with

18   the changes to the clinical trial protocol, in the

19   next few slides.

20        The original version of the protocol was

21   finalized on May 10, 2010.  This version was not

22   submitted to the FDA as the study was not yet

1    initiated in the U.S. at this time.  Version 2 of

2    the protocol, dated September 22, 2010, was

3    submitted to the FDA to support enrollment of

4    patients from U.S. sites.  Comments on the protocol

5    were not requested at that time.

6        In April of 2011, the applicant submitted

7    version 3 of the protocol, which included changes

8    to the inclusion and exclusion criteria, mainly to

9    liberalize the criteria to allow for expanded

10   enrollment of patients with single-vessel disease

11   in a major coronary artery.  Previously it only

12   allowed patients with multi-vessel disease.

13       At that time, approximately 1200 individuals

14   had already been randomized.  As illustrated here,

15   this change was made prior to the interim analysis.

16   The applicant reported that these changes were made

17   based on advice received from the steering

18   committee.

19       Version 4 of the protocol was finalized

20   December 2011, and submitted to the FDA in January

21   of 2012.  The changes made in this version were in

22   response to the discussions that occurred between

1    the applicant and the FDA with respect to version 2

2    of the protocol.  At that time, 3400 individuals

3    had been randomized into the trial.

4         Many important changes were made in this

5    version of the protocol.  Some of these changes

6    reflected advice received from the FDA related to

7    the overall cardiovascular risk assessment strategy

8    for empagliflozin, and included changes to the

9    sample size and anticipated trial duration.

10        This change was made to ensure that at least

11   691 MACE events would be captured in the EMPA-REG

12   study.  From this point onward, the trial was

13   powered to independently exclude the post-approval

14   1.3 cardiovascular risk margin.

15        Additional changes included specifying that

16   silent MI would be excluded from the primary

17   endpoint.  This version also specified that the

18   within-trial interim analysis to assess for 1.3

19   would be carried out, and that type 1 error would

20   be controlled to account for this analysis.

21        All these changes to the protocol occurred

22   prior to the interim analysis, as you can see from

1    the timeline.  While the FDA agreed with the

2    general changes, the issue of silent MI was not

3    specifically discussed.

4         Finally, version 5 made some specific

5    changes to require that ECG be reviewed by

6    investigator, change the follow-up period from 4

7    weeks to 30 days, and added adjudication for

8    malignancies and hepatic events to address

9    potential safety concerns.

10        While I have limited my discussion of the

11   protocol changes to the major revisions, it is also

12   worth noting that there were changes to secondary

13   and tertiary exploratory endpoints.

14        I will now discuss the changes to the CEC

15   charter.  The CEC charter contained the endpoint

16   definitions to be used in the adjudication process.

17   I will focus on changes that were made to endpoint

18   definitions over the course of the trial.

19        The original CEC charter was created prior

20   to the initiation of the EMPA-REG study for use

21   with another anti-diabetic development program.

22   The empagliflozin program was added to the existing

1 CEC charter.  There were at least nine versions of

2 the CEC charter, and here I will limit my

3 discussion to changes that are potentially relevant

4 to the interpretation of cardiovascular outcomes.

5   Changes to the endpoint definitions were

6 made in version 6 of the charter.  Selected changes

7 are presented on the slide.  The myocardial

8 infarction definition was liberalized from

9 requiring symptoms of ischemia and two supportive

10 criteria, ECG, biomarker, or imaging, to requiring

11 symptoms of ischemia, and only one additional

12 supportive criterion.

13   Also, the cardiac biomarker elevation

14 criterion was changed from one requiring the

15 99 percentile of the upper reference limit to one

16 requiring that cardiac biomarker be found to be

17 above the upper reference limit for assay.

18   The hospitalization for unstable angina and

19 hospitalization for heart failure were also

20 expanded to allow for overnight admission to chest

21 pain observation units in addition to emergency

22 room visits and hospital admissions.  The stroke

1  definition only had minor modifications.

2  These changes were implemented prior to the

3  interim analysis, were dated February 18, 2012, and

4  were made at the recommendation of the CEC members.

5  The definition of hospitalization for heart

6  failure was again changed in version 8 of the CEC

7  charter on April 4, 2014.  This change further

8  liberalized the definition and allowed for

9  inclusion of hospitalization for heart failure

10  events if oral diuretics had been increased or

11  initiated.  Prior to that, only events resulting in

12  initiation or increase in IV therapies qualified.

13  This definition change occurred after interim data

14  unblinding.

15  In version 9 of the charter, dated December

16  2014, subdural hematoma was removed from the

17  definition of ischemic stroke.  Although the

18  endpoint definitions changed significantly during

19  the trial, events were adjudicated according to the

20  applicant based on the last definitions.

21  It should be noted that some definitions

22  differ significantly from the current standardized

1    definitions for cardiovascular disease and stroke

2    endpoints, and in particular the definition for

3    hospitalization for heart failure.  The impact of

4    these changes on study results could not be

5    quantified retrospectively.

6        I will now discuss key changes made to the

7    statistical analysis plan for this trial.  The

8    statistical analysis plan for the EMPA-REG study

9    was finalized prior to the interim analysis.  In

10   the initial statistical analysis plan, dated

11   August 24, 2012, the primary endpoint was listed as

12   3-point MACE, which is a composite of

13   cardiovascular death, non-fatal myocardial

14   infarction excluding silent MI, and non-fatal

15   stroke.

16       The secondary endpoint was 4-point MACE,

17   which is a composite of cardiovascular death,

18   non-fatal MI excluding silent MI, non-fatal stroke,

19   and hospitalization for unstable angina.  Silent MI

20   and heart failure requiring hospitalization were

21   other secondary endpoints.

22       A revised statistical analysis plan, dated

1    May 2015, was received in November 2015.  The plan

2    did not make any changes to the primary and

3    secondary endpoints, but added a significant number

4    of other exploratory endpoints, some of which I

5    will discuss later in this presentation.

6         This version, for the first time, specified

7    the silent MI definition that was to be used for

8    analysis.  The statistical analysis plan also added

9    language to clarify that non-assessable deaths are

10   presumed to be CV death and therefore included in

11   the analysis of the primary and secondary

12   endpoints.

13        I will now describe baseline demographic and

14   disease characteristics of the study population and

15   summarize the disposition of the participants.

16   Baseline demographic characteristics and diabetes

17   history were generally balanced in the analysis

18   population.

19        In both arms, the mean age of the study

20   participants was 63 years, and the mean hemoglobin

21   A1c was 8.1 percent.  The majority of subjects had

22   been diagnosed with type 2 diabetes for more than 5

1   years, with over half of subjects diagnosed for

2   more than 10.  The proportion of patients reporting

3   diabetic complications was also balanced between

4   the treatment groups.

5       The treatment groups were also similar in

6   terms of baseline cardiovascular disease history.

7   The history of coronary artery disease was present

8   in around 76 percent of individuals at trial entry,

9   and almost half of the subjects reported a history

10  of past myocardial infarction.  Around 23 percent

11  of patients had a history of stroke, and around 21

12  percent a history of peripheral artery disease.

13      I will now turn to participant disposition.

14  My slide shows participants in the analysis

15  population, which excludes participants from sites

16  with significant good clinical practice violations

17  and 8 individuals who were randomized but never

18  treated.

19      In the analysis population, 7,020 subjects

20  were randomized and treated with at least one dose

21  of the intervention.  Information on MACE was

22  available for 6,809 subjects at the end of the

study, or approximately 97 percent of the original

cohort.  211 subjects prematurely discontinued the

trial and did not have complete data on 3-point

MACE.  These individuals account for the missing

information on MACE.

Information on vital status was available

for 6,967 subjects, approximately 99.2 percent of

the original cohort.  Only 53 subjects did not have

information on vital status.  These individuals

account for the missing information on death in

this study.

I will now turn the presentation over to our

biostatistician, Dr. Jennifer Clark, to review the

statistical assessment of the EMPA-REG safety

trial.

**FDA Presentation - Jennifer Clark**

DR. CLARK:  Thank you.  Good morning.  My

name is Jennifer Clark.  I will be giving a

presentation with the statistical assessment of the

EMPA-REG trial.  I'll start with a brief overview

of aspects from the trial that were important for

the statistical assessment.  This includes the

1    analysis population, trial duration, and

2    statistical methods.

3         I will go over the trial results and the

4    testing hierarchy that was used to preserve the

5    type 1 error.  In order to understand the results,

6    we will take a closer look at the primary 3-point

7    MACE results and the components that make up this

8    composite endpoint.  I will also consider all-cause

9    mortality within the trial, as well as follow up

10    for mortality and cardiovascular MACE endpoints.

11    Sensitivity analysis results will be shown for both

12    MACE and death.

13         This trial was part of a diabetes drug

14    requirement to rule out a 30-percent increase in

15    cardiovascular risk when compared to placebo.  This

16    is the first of the diabetes safety trials where

17    superiority is being considered for what were

18    initially safety endpoints.

19         The duration of this trial was less than

20    five years, with first randomization occurring on

21    September 15, 2010, and the last on April 19, 2013.

22    Those with last study visits on or after

1    December 15, 2014 were considered completers for

2    the study.

3         The primary objective of this trial was to

4    demonstrate safety with non-inferiority of

5    empagliflozin against placebo for major adverse

6    cardiovascular events, or MACE.  Type 1 error was

7    controlled for multiplicity through a prespecified

8    testing hierarchy.  This hierarchy only controlled

9    error for the 3 point and 4-point MACE endpoints.

10        The first step in the hierarchy was testing

11   an increase in CV events using a non-inferiority

12   margin of 1.3 for 3-point MACE.  If a 30 percent

13   increase in CV events with 3-point MACE is ruled

14   out in the first step, then 4-point MACE would be

15   tested using the same non-inferiority margin.  If a

16   30 percent increase in CV events was ruled out for

17   both MACE endpoints, then similar methodology could

18   be used to test for superiority, first for 3-point

19   MACE, and then 4-point MACE.

20        Patients were randomized to either placebo,

21   10 milligrams of empagliflozin, or 25 milligrams of

22   empagliflozin.  The treated set was prespecified

1    for the primary analysis.  There were 8 subjects,

2    which were randomized to a treatment arm but failed

3    to start treatment, so they were not included in

4    the primary analysis.  There was 37 subjects who

5    started treatment but were excluded due to site

6    non-compliance or other issues.  The two

7    empagliflozin treatment arms were prespecified to

8    be pooled together for the primary analysis.

9        A Cox proportional hazard model was used for

10   the primary analysis.  The model included adjusting

11   baseline covariates for age, sex, BMI, HbA1c, eGFR,

12   and geographic region, along with study treatment.

13   Hazard ratios were based on Cox model results.

14       There was an additional adjustment to the

15   type 1 error due to the prespecified interim

16   analysis, which had a data cutoff of June 22, 2012.

17   Because of this, the final analysis results here

18   will be based on 95.02 percent confidence intervals

19   instead of the usual 95 percent confidence

20   intervals.

21       Here, I will be presenting the MACE results

22   within the prespecified testing hierarchy.  In

1    order to be considered non-inferior to placebo, the

2    upper bound of the 95.02 percent confidence

3    interval for the hazard ratio had to be below 1.3.

4    When testing for superiority against placebo, a

5    similar methodology is used with the upper bounds,

6    but here the bound must be less than 1.

7          Three-point MACE has a hazard ratio of 0.86

8    with an upper bound of 0.99.  4-point MACE has a

9    hazard ratio of 0.89 with an upper bound of 1.01.

10   When looking at this in the testing hierarchy, we

11   see the first hypothesis for ruling out a

12   30 percent increase in CV events is met since the

13   upper bound for 3-point MACE is below 1.3.

14   Non-inferiority against placebo for 4-point MACE is

15   also achieved since this upper bound is also below

16   1.3.

17          The next step in the hierarchy is to move to

18   testing for superiority.  Since the upper bound for

19   3-point MACE is below 1, the criteria for showing

20   superiority is met for this endpoint.  This means

21   this result supports cardiovascular benefit when

22   comparing empagliflozin to placebo.  This is

1  important because it's what the efficacy claim is

2  based upon.

3       When we progress to the last step in the

4  hierarchy, we see that superiority is not met for

5  the 4-point MACE endpoint since the upper bound is

6  not below 1, but non-inferiority still holds.  At

7  this point, all alpha for type 1 error is

8  considered lost.

9       Formal statistical testing would stop here

10 had there been any further hypotheses prespecified

11 in the hierarchy.  Since the 4-point MACE endpoint

12 did not attain superiority, it will not be further

13 discussed in this presentation.

14      Kaplan-Meier curves of the 3-point MACE

15 endpoint for both the pooled empagliflozin arms and

16 the placebo arm are shown here with the number

17 remaining at risk at the bottom of the table.  We

18 see a separation of the curves around 3 months,

19 which continues throughout the study.

20      The total number of patients experiencing a

21 MACE event during the study period was 490 for

22 empagliflozin and 282 for placebo.  Since the

1 number of patients in the pooled empagliflozin arms

2 was approximately double the amount on placebo,

3 this translates to 12.1 percent of subjects having

4 a MACE on placebo and 10.5 percent of subjects with

5 MACE on empagliflozin.

6 Three-point MACE is a composite made up of

7 CV death, none-fatal MI, and non-fatal stroke.  In

8 order to understand what this and the primary

9 hazard ratio results actually mean we need to look

10 at these and the related counterpart outcomes.

11 The first component of CV death had the

12 largest difference between treatment arms and the

13 number of patients experiencing an event; 172 or

14 3.7 percent of patients had a CV death in the

15 empagliflozin group versus 137 or 5.9 percent of

16 those on placebo.

17 When looking at the related endpoint of

18 all-cause death, of which CV death is a subset, we

19 see that the difference in the number of patients

20 experiencing an event is proportionally similar

21 between the two treatment arms; 5.7 percent of

22 subjects on empagliflozin died versus 8.3 percent

1    on placebo.

2          The second component of 3-point MACE was

3    non-fatal MI.  While there were more of these

4    events in total than there were of CV deaths, they

5    were not as disproportionately dispersed between

6    the two treatment arms; 4.5 percent of patients on

7    empagliflozin experienced a non-fatal MI versus 5.2

8    percent on placebo.

9          This close disbursement of events was

10   similarly mirrored when looking at patients who

11   experienced any sort of MI event, fatal or

12   non-fatal, with 4.8 percent experiencing an MI on

13   empagliflozin and 5.4 percent on placebo.

14         The third component of 3-point MACE was

15   non-fatal stroke.  This had the smallest number of

16   events with a slight imbalance favoring placebo;

17   3.2 percent of subjects on empagliflozin

18   experienced a non-fatal stroke versus 2.6 percent

19   on placebo.

20         This imbalance is again reflected in the

21   related outcomes of all strokes.  Here, we have

22   3.5 percent of subjects on empagliflozin

1   experiencing a stroke versus 3 percent on placebo.

2   It is clear from these figures that the biggest

3   difference between the treatment arms lies in the

4   CV death component, which favors empagliflozin.

5         The estimated incidence rate is based on the

6   number of events, shown on the previous slides, and

7   the total number of patient years observed in the

8   study.  For the primary 3-point MACE endpoint,

9   there were 3.7 events per 100 patient years on

10  empagliflozin and 4.4 per 100 patient years on

11  placebo.

12        The difference between the treatment arms

13  for the estimated incidence in each of the

14  components reflects the differences that were seen

15  in the number of events in the treatment arms.  CV

16  death and its corresponding all-cause death outcome

17  show the greatest difference between treatment

18  arms.

19        We used the same Cox proportional hazards

20  model from the primary analysis to estimate hazard

21  ratios and 95 percent confidence intervals for each

22  of the components of 3-point MACE.  The results are

1   shown here on this plot with a line drawn at 1 to

2   show where hazard rates would be considered the

3   same between the two treatment arms.  The hazard

4   ratios are in line with what we would expect based

5   on the number of events occurring in each arm.

6           The primary 3-point MACE endpoint is shown

7   in blue with each of its components in maroon.

8   Both non-fatal stroke and non-fatal MI have upper

9   bounds that are greater than 1.  The superiority

10  result for 3-point MACE is clearly due to the

11  imbalance of events seen in CV death.

12          The results from the MACE components also

13  translate to the related endpoints of all strokes,

14  all MIs, and all-cause death.  This plot shows the

15  Cox model results for these related outcomes.

16  Given that the ratio of patients experiencing an

17  event was similar to the corresponding MACE

18  component, results here are comparable to these

19  related endpoints.

20          The results for CV death, which had a hazard

21  ratio of 0.62 with an upper bound of 0.78, is also

22  reflected in all-cause death with a hazard ratio of

1    0.68 and an upper bound of 0.82.

2        Since the death results were found to be the

3    main factor for the MACE findings, we will be

4    looking more closely at this.  An inherent flaw in

5    the prespecified primary analysis is that those who

6    have a non-CV death are assumed to have a time

7    until MACE equal to those who are alive and

8    censored in the same treatment arm.  For the

9    EMPA-REG trial, this bias favored the placebo arm.

10        There were 154 non-CV deaths, of which 19

11    subjects had a non-fatal MACE, so there were 135

12    additional events when including all-cause death in

13    the MACE endpoint, 51 on placebo and 84 on

14    empagliflozin.  This led to a hazard ratio of 0.85

15    with an upper bound of 0.97.

16        The Kaplan-Meier plots for CV death and

17    all-cause death are seen here.  We again see a

18    separation of the curve starting out within the

19    first few months of the study, like what was seen

20    in 3-point MACE.  The overall estimated incidence

21    for CV death was 2.02 for the placebo arm and 1.24

22    for the pooled empagliflozin arm.  When looking at

all-cause death, this went up to 2.86 for placebo

and 1.94 for empagliflozin.

We examined follow-up in the trial for both

MACE and death, which will be presented along with

sensitivity analyses.  There were approximately 2.9

percent of patients, which prematurely discontinued

for MACE in the placebo arm, and 3.1 percent in the

pooled empagliflozin arm.

Follow-up for death was more complete with

0.73 percent on the placebo arm prematurely

discontinued, and 0.77 percent in the empagliflozin

arm.  Premature discontinuation did not seem to

affect the overall picture of empagliflozin.

Sensitivity analyses for 3-point MACE were

run using multiple imputation for the missing

follow-up in those prematurely discontinued.  The

assumed event rate for the missing follow-up until

December 15, 2014 was equal to the estimated

incidence in the off-treatment patients of the

empagliflozin and placebo groups.

Results from this analysis using the imputed

and observed data were relatively unchanged from

1   the primary analysis results.

2        Sensitivity analyses using an extreme

3   scenario favoring the placebo arm for CV death and

4   death were also run.  Results from these analyses

5   showed an upper bound that remained below 1.  These

6   results are based on a single cardiovascular

7   outcome trial, which was required to allow a

8   30 percent increase in cardiovascular risk.  This

9   trial was a success in ruling out the 30 percent

10   increase for both the primary 3-point and secondary

11   4-point MACE endpoints.

12        Additionally, the trial showed superiority

13   against placebo for 3-point MACE only.  Currently,

14   there is no precedent for when these types of

15   safety studies show superiority.  The superiority

16   of the 3-point MACE is due to the differences seen

17   between the treatment arms and CV death.  When

18   examining the amounts of premature discontinuation

19   for this, we did not find that it affected the

20   results.

21        Thank you.  And I will turn this back to Dr.

22   Lungu.

1          DR. LUNGU:  Thank you, Dr. Clark.  I will

2     now discuss some additional issues related to the

3     primary endpoint finding.  While the results of the

4     primary analysis demonstrated a statistically

5     significant effect of empagliflozin on 3-point

6     MACE, there are important additional

7     considerations, which were needed to be weighed

8     when deciding whether this trial provides the level

9     of evidence necessary to form the basis for a new

10    claim.

11          I covered the conduct of the trial in my

12    previous presentation, and I am now going to cover

13    some issues that are specifically related to the

14    interpretation of the results.  These issues

15    attempt to address the following two questions.

16    Did the trial win on the primary endpoint, which is

17    arguably the gatekeeper for looking at

18    cardiovascular death, a component of the primary

19    endpoint?  And does the trial provide substantial

20    evidence of effectiveness in reducing

21    cardiovascular mortality?

22          Perhaps the most obvious consideration is

1    that the EMPA-REG study was a single study, and as

2    you have heard this morning, two studies are

3    generally needed to form the basis for a new claim.

4    The EMPA-REG study was also primarily designed to

5    rule out excess cardiovascular risk and not

6    specifically to establish a benefit.  In that

7    sense, it is a new paradigm and the persuasiveness

8    of the evidence generated by such a trial could be

9    affected.

10           It may also be relevant to consider that the

11   trial was primarily focused on evaluating a

12   specific type of cardiovascular risk.  The p-value

13   for superiority regarding the 3-point MACE endpoint

14   was 0.04.  As you have heard this morning from

15   Dr. Guettier, the level of evidence for a single

16   trial needs to be very statistically persuasive.

17   You will need to consider whether the statistical

18   results represent a very statistically persuasive

19   finding and whether their persuasiveness is

20   sufficient to form the basis for a new claim.

21           Dr. Clark has reviewed the impact that

22   missing data had on the trial's statistical

1    significance.  There may be other clinical issues,

2    such as handling of the silent MIs, which could

3    also impact your level of confidence in the primary

4    results.  This will be discussed in a later part of

5    my presentation.

6        As you have also heard, the MACE result

7    appears entirely driven by the effect of

8    empagliflozin on cardiovascular mortality, with

9    little effect on non-fatal stroke or MI.  This

10   suggests the benefit of empagliflozin may not

11   reflect atherosclerotic cardiovascular risk

12   reduction, the main risk evaluated in this trial.

13       In the next few slides, I will focus on two

14   specific clinical issues, which may impact your

15   level of confidence in the results.  One is the

16   potential lack of complete ascertainment for some

17   myocardial infarction events, namely silent MI

18   events.  The second is an absence of information to

19   confirm that the large proportion of cardiovascular

20   deaths were indeed cardiovascular deaths.

21       I will now discuss the myocardial infarction

22   endpoint focusing on the issue of the silent

myocardial infarction.  Like clinical MI, a true

clinical event of silent MI is associated with poor

prognosis, and is a clinically important morbid

event.  Diabetic patients may be particularly prone

to these events as they may not present with

typical clinical symptoms associated with MI due to

their underlying disease.

Because this event is an asymptomatic event,

it is a challenging event to capture, fully

ascertain, and analyze in a cardiovascular outcomes

trial.  In terms of precedent, some applicants have

included these events in their primary endpoint

while others have not.  To some extent, this has

depended on the types of procedures in place to

prospectively capture these events.

The EMPA-REG study design suggests that the

applicant, at least initially, intended to collect

silent MI events.  With regard to trial planning,

silent MI was an event initially defined in the

clinical trial protocol and ECGs were collected

routinely at prespecified intervals throughout the

trial.  In addition, a central ECG vendor was

1   retained to analyze ECG changes and flag concerning

2   changes to investigators.

3   Moreover, the case report forms included

4   silent MI as an outcome event to be sent for

5   adjudication.  The adjudication committee was to

6   evaluate events, which could be consistent with the

7   primary endpoint, and silent MI was a trigger event

8   that should have been evaluated.

9   In the nine versions of the CEC charter

10  reviewed, we did not identify a specific definition

11  for silent MI.  Potential outcome events coded to

12  the preferred term of silent MI, and referred to

13  adjudication, had to fit one of the MI definitions

14  in the charter to be counted as a primary endpoint

15  event.

16  Silent MI was designated as a secondary

17  endpoint in the protocol, but it is unclear whether

18  these events were to be included in the primary

19  endpoint, as these were not explicitly excluded

20  from the initial versions of the protocol.

21  In version 4 of the protocol, which was

22  implemented in 2011, the applicant explicitly

1    specified that silent MI was not to be counted as

2    part of the non-fatal MI component in MACE.  This

3    occurred prior to the interim analysis.

4         The final statistical analysis plan, which

5    was implemented in 2015, completely redefined

6    silent MI and changed it from a clinical event to

7    an event purely based on ECG criteria.  As I have

8    mentioned, the CEC was to adjudicate investigator-

9    reported silent MIs, but the provided definitions

10    in the CEC charter did not include a specific

11    definition for silent MI.  The CEC adjudication

12    committee asked the applicant for clarification

13    with regard to silent MI, and it is not clear that

14    a response was ever provided.

15         As I have said, the final event definition

16    for silent MI used in analysis was implemented in a

17    2015 change to the statistical analysis plan.  This

18    was to be used in secondary analysis only, and is

19    based on ECG criteria.  I would like to stress that

20    this definition of events did not include any input

21    from investigators or adjudicators, and is subject

22    to these very important limitations.

1          Only about half of the analysis population

2     had data that could be evaluated for the occurrence

3     of silent MI using the applicant's definition.

4     This was because of ECG abnormalities at baseline,

5     absence of post-baseline ECG evaluations, or

6     occurrence of intervening ECG changes unrelated to

7     silent MI event in some participants.  This further

8     limits the conclusion that can be drawn from this

9     endpoint.

10          We did explore the impact of inclusion of

11    these events as defined by the applicant in the

12    primary endpoint, and I will show you this on the

13    next slide.  Of the 7,020 subjects in the analysis

14    population, only 3,589 had data that could be

15    assessed for a silent MI based on the applicant's

16    final definition.  Using this definition, 15 events

17    were identified in placebo and 38 in the

18    empagliflozin group.  The incidence of silent MI

19    was slightly higher in the empagliflozin group at

20    1.6 percent compared to 1.2 percent in placebo.

21          Acknowledging that there are major

22    limitations to these data, inclusion of the silent

1    MI in the primary endpoint data leads to rejection

2    of superiority for 3-point MACE.  The division

3    concludes that there is missing information on

4    clinically meaningful silent myocardial infarction

5    events in the EMPA-REG OUTCOME study.

6         We would like you to opine on whether the

7    absence of reliable information on silent MI is

8    important in your overall assessment of the

9    persuasiveness of the primary results.

10         The second topic that may impact the

11   persuasiveness of the results is related to the

12   cardiovascular death findings, and specifically

13   related to the large proportion of cardiovascular

14   deaths, which were deemed non-assessable by

15   adjudicators.

16         In the assessment of death, adjudicators

17   were tasked with assigning the cause of death to

18   either a cardiovascular or a non-cardiovascular

19   cause.  Deaths assessed as cardiovascular death

20   were further subcategorized as shown in the table.

21   As Dr. Clark discussed, fewer deaths were observed

22   in the empagliflozin group.  The difference was

1   primarily due to deaths categorized as

2   cardiovascular death.

3        The largest subcategory for cardiovascular

4   death was non-assessable death.  This subcategory

5   made up 40 percent of events, and was followed only

6   by sudden cardiovascular death and death due to

7   heart failure or cardiogenic shock as the most

8   frequent causes of CV death.

9        Given the proportion of events that were

10   reported as non-assessable, it is unclear whether

11   all events were truly cardiovascular death events,

12   or what potential mechanism is responsible for the

13   observed reduction in cardiovascular death.

14        In cardiovascular outcome trials, it is

15   generally acceptable to categorize non-assessable

16   death as presumed to be cardiovascular death,

17   however the expectation is that this category would

18   represent only a small proportion of these events.

19   This is not the case in the EMPA-REG OUTCOME study.

20        Given the relatively large proportion of

21   non-assessable deaths in the EMPA-REG study, we

22   examined the type of information available to

1   adjudicators on these events.  Less than half of

2   the patients had a death certificate or proof of

3   death available, and none had autopsy.  Although

4   the preferred terms reported by investigators for

5   these patients were suggestive of cardiovascular

6   death in the majority of cases, there is really no

7   information to confirm or refute this from the

8   trial documents.

9         Given the uncertainty around these deaths,

10  we analyzed the impact of excluding non-assessable

11  death on 3-point MACE and cardiovascular death.

12  Excluding non-assessable death from the primary

13  endpoint changes the results from superior to no

14  longer superior.

15        The hazard ratio for 3-point MACE excluding

16  these deaths is 0.9 with a 95 confidence interval

17  of 0.77 to 1.06.  Excluding non-assessable death

18  from analysis of cardiovascular death would not

19  alter conclusions on cardiovascular death where the

20  hazard ratio not including these events is 0.59

21  with a 95 percent confidence interval of 0.44 to

22  0.79.

1       We would like you to opine on how these

2   events impact your interpretation of the

3   persuasiveness of the results.

4       I will next discuss the exploratory

5   endpoints of heart failure and renal endpoints.  I

6   will start with heart failure.  As a reminder, the

7   hospitalization for heart failure definition was

8   liberalized over the course of the trial to allow

9   for the addition of oral diuretic, as well as

10  short-term stays in chest pain observation units.

11      This made the definition less specific and

12  potentially allows for inclusion of episodes that

13  were either milder forms of heart failure or not

14  heart failure at all.  The definition used in

15  analysis is less specific and represents less

16  severe events than the current standardized

17  definition.

18      Analysis for hospitalization for heart

19  failure events were purely exploratory in this

20  trial, and type 1 error was not controlled.  The

21  direction of change in the results of analysis

22  suggest that treatment with empagliflozin could be

1    associated with a decrease in risk for

2    hospitalization for heart failure or

3    hospitalization for heart failure and death due to

4    heart failure.

5    In addition to the exploratory nature of

6    these analyses, the agency has other reservations

7    with regard to the adequacy of this study to

8    definitively establish a benefit of empagliflozin

9    on heart failure and heart failure outcomes.

10    One reservation is that the study was not

11    designed with the specific intent of demonstrating

12    an effect on heart failure.  Only 10 percent of

13    subjects had a reported history of heart failure at

14    baseline.

15    For subjects with a history of heart

16    failure, information on the type of heart failure

17    and the severity of heart failure was not

18    collected.  For example, there are no data on

19    ejection fraction or New York Heart Association

20    functional classification for these patients.

21    Furthermore, it is not clear how well heart failure

22    was managed at baseline and throughout the study.

1          While a majority of patients were receiving

2     renin-angiotensin system antagonist and beta

3     blockers, there are no data to evaluate whether the

4     dose of these drugs and other drugs used in the

5     chronic management of heart failure were optimized.

6     While the heart failure findings are interesting,

7     the division believes that data on heart failure

8     are exploratory and should be confirmed in studies

9     designed to specifically assess this outcome.

10          I will now discuss the results based on

11    renal-related endpoints and the issues that affect

12    the interpretability of the results.  The applicant

13    proposed changes to the prescribing information to

14    reflect the results of these analyses.

15          Analyses based on renal endpoints were

16    exploratory in the EMPA-REG study.  There was no

17    plan to control for type 1 error rate across these

18    analyses in any version of the protocol or

19    statistical analysis plan.

20          The definitions for various renal endpoints

21    were changed significantly throughout the trial.

22    Specifics of renal endpoints to be used in the

1   final analysis were defined late in the trial in

2   the final statistical analysis plan submitted after

3   the interim analysis, and after the trial had

4   ended.

5        In addition, the clinical trial protocol or

6   statistical analysis plan did not specify processes

7   for identifying or confirming potential renal

8   events.  These endpoints were identified based on

9   investigator-reported adverse events or in

10   laboratory findings, and were not adjudicated.

11        I will next discuss the results and

12   interpretation of the renal endpoints analysis.

13   Exploratory renal endpoints used for the final

14   analysis included new onset albuminuria, new onset

15   macroalbuminuria, and the composite endpoint new or

16   worsening nephropathy, which included new onset

17   macroalbuminuria, doubling of creatinine with eGFR

18   less than 45, initiation of continuous renal

19   replacement therapy, and death due to renal

20   disease.

21        I will first discuss the albuminuria related

22   endpoints, followed by the composite of new or

1    worsening nephropathy.  Albuminuria was assessed

2    using a single spot urine albumin to creatinine

3    ratio measured by a central laboratory.  The

4    analysis for new onset albuminuria included

5    subjects without albuminuria at baseline.

6          Similarly, the analysis for new onset

7    macroalbuminuria included subjects without

8    macroalbuminuria at baseline.  No notable

9    difference was observed between treatment groups

10    for new onset albuminuria.  New onset

11    macroalbuminuria was more frequent in the placebo

12    group.

13          Because empagliflozin causes intravascular

14    volume contraction, we explored the potential

15    impact of hemodynamic effects on urine albumin

16    excretion.  I will show this in the next slides.

17    This slide shows changes in spot urine albumin to

18    creatinine ratio over the course of the trial.  It

19    suggests lower albuminuria in the empagliflozin

20    group.

21          The changes in glomerular filtration ratio

22    and systolic blood pressure suggests an acute

1 hemodynamic effect with empagliflozin, as shown by

2 the acute drop in eGFR shown on the left, and the

3 acute decrease in systolic blood pressure shown on

4 the right.  The changes in eGFR and systolic blood

5 pressure suggests that changes in albuminuria could

6 be driven by these factors.

7 The effect on albuminuria reflects a

8 pharmacodynamic effect.  This slide shows urine

9 albumin to creatinine ratio at baseline, last value

10 on-treatment, and after a 30-day wash-out.  The

11 effect of empagliflozin on albumin to creatinine

12 ratio appears to go away with wash-out, as

13 illustrated by the increase in urine albumin to

14 creatinine ratio from the last value on-treatment

15 to 30-day follow-up.  This suggests that the

16 underlying renal disease is not changed.

17 The applicant used a composite endpoint

18 consisting of new onset macroalbuminuria, doubling

19 of serum creatinine with eGFR less than 45,

20 initiation of continuous renal replacement therapy,

21 and death due to renal disease, to define an event

22 of new or worsening nephropathy.  Using this

1   definition, fewer patients in the empagliflozin

2   group seemed to experience this endpoint.  I would

3   note that the component that contributes the most

4   to this difference is new onset macroalbuminuria.

5        As I mentioned previously, this may be in

6   great part attributable to the hemodynamic effect

7   with empagliflozin.  The other components

8   contributed a small number of events, and 2 out of

9   4 components had too few events to draw any

10   meaningful conclusions.

11        I will review my concerns regarding the

12   components of doubling of serum creatinine and

13   renal replacement therapy over the next few slides.

14   I will not be discussing death due to renal disease

15   as there were only three events reported in the

16   trial.

17        The doubling of serum creatinine was used as

18   a marker of diabetic kidney disease progression.

19   This criterion required only a single post-baseline

20   serum creatinine value more than twice baseline,

21   with an eGFR less than 45 on the same date without

22   confirmation that the decline in renal function

1    persisted after a specified time period.

2          As a result, the endpoint might capture both

3    acute reversible changes in renal function, such as

4    acute kidney injury, and chronic irreversible

5    changes in renal function, such as developmental

6    progression of chronic kidney disease.

7          To explore this issue, we look for a

8    confirmatory creatinine value more than twice

9    baseline and eGFR less than 45 at any time in the

10    30 days following an initial event.  The decline

11    was confirmed in fewer than half of subjects with

12    an event, suggesting that most of the initial

13    events may have been cases of acute kidney injury.

14    This endpoint does not appear to be specific in

15    capturing events of nephropathy as defined by the

16    applicant.

17          I will now discuss the evaluation of events

18    classified by the applicant as continuous renal

19    replacement therapy.  The definition of this

20    endpoint was not clearly specified, and we reviewed

21    the narratives and CRFs for a random sample of

22    events to gain additional insight.  Most of the

1    cases reviewed represented events of acute kidney

2    injury requiring temporary dialysis, and none of

3    them represented chronic dialysis that could be

4    attributed to progression of underlying kidney

5    disease.

6          This suggests that in EMPA-REG, this

7    endpoint was not able to differentiate between

8    acute reversible need for renal replacement therapy

9    and end-stage renal disease.  While acute kidney

10    injury events requiring dialysis are clinically

11    significant, they do not necessarily represent

12    events attributable to diabetic nephropathy disease

13    progression.

14          In conclusion, renal endpoints in EMPA-REG

15    were exploratory.  There was no control of type 1

16    error.  The endpoints selected differ from those

17    typically used to establish efficacy of drugs to

18    treat diabetic nephropathy or to assess effects on

19    irreversible loss of renal function.

20          The endpoints were redefined during the

21    trial and processes to identify and confirm renal

22    events were not defined.  The endpoints captured

effects on albuminuria, which appear to be a

reversible hemodynamic effect, and may not predict

treatment effects on renal outcomes.

The agency has not accepted on-treatment

effects on albuminuria as a surrogate for clinical

outcomes in diabetic nephropathy, in part because

therapies can have acute reversible pharmacologic

effects on albuminuria that may differ from the

long-term effects on the irreversible loss of renal

function and underlying disease progression.

Having completed my discussion of

exploratory endpoints, I will turn next to

highlight some differences that we noticed between

the treatment arms.  The study was designed to

compare empagliflozin to placebo in addition to

local standard of care.  The expectation is that

this would minimize confounding in the

interpretability of the results.

Glycemic control was different between the

treatment arms.  While an early difference in

glycemic control was expected, given that one group

was randomized on active drug while the other group

1  was not, it was expected that adjustment of co-

2  administered anti-diabetic therapy would minimize

3  differences as the trial progressed.  However, as

4  seen on this slide, the difference persisted over

5  the entire course of the trial.

6      The reason for this difference is unclear.

7  Anti-diabetic therapies appear to have been

8  intensified more in the placebo group, yet these

9  changes did not result in minimizing glycemic

10  control differences.  Background therapies were

11  increased more, and new anti-diabetics were started

12  more frequently in the placebo-treated subjects.

13  Insulin DPP-4 inhibitors and sulfonylureas were the

14  most frequently used concomitant anti-diabetics.

15      As observed in the original submission,

16  small dose-dependent increases in mean cholesterol

17  were seen with empagliflozin.  In addition, small

18  increases in hemoglobin and hematocrit were

19  observed and more patients shifted from normal

20  hemoglobin or hematocrit to values above the upper

21  limit of normal.

22      As expected, based on blood pressure

1     differences, more patients in the placebo group had

2     anti-hypertensive medications added during the

3     trial.  However, despite the increase in

4     cholesterol with empagliflozin, fewer patients in

5     the empagliflozin group received additional

6     lipid-lowering medications over the course of the

7     trial.

8          I will next talk about the cardiovascular

9     safety issue we have been monitoring for this

10    product class, namely the risk of stroke events.  I

11    remind you that strokes were collected as part of

12    the primary endpoint and that the results showed a

13    numerical imbalance not favoring empagliflozin for

14    this event.

15         A numerical imbalance was also seen with the

16    other two members of the class at the time of the

17    approval and appears inconsistent with the observed

18    findings of blood pressure lowering with this

19    agent.

20         The adjudication of stroke in the EMPA-REG

21    study was based on all available data.

22    Standardized assessments for stroke events, such as

1    clinical assessment or specific imaging, were not

2    required or specified in the protocol or the CEC

3    charter.  The CEC charter outlined four criteria

4    for identification of stroke.

5          There needed to be a rapid onset of a focal

6    or global neurological deficit.  The deficit needed

7    to last for more than 24 hours, unless it met the

8    criteria shown in parenthesis.  The deficit could

9    not be attributed to a non-stroke cause, such as

10    brain tumor or head trauma.  Finally, the diagnosis

11    needed to be confirmed either by a specialist by

12    imaging or by lumbar puncture.

13          Two hundred and thirty-three strokes were

14    observed with 210 of these reported as non-fatal

15    strokes.  More strokes occurred in the

16    empagliflozin group, and the hazard ratio for

17    stroke, including fatal and non-fatal stroke, and

18    for non-fatal stroke alone, was about 1.

19          These findings raise question with regards

20    to the role of empagliflozin on reduction of

21    atherosclerotic cardiovascular disease progression

22    and cannot definitively exclude the possibility

1    that the drug could cause a small increase in the

2    risk of stroke events in certain individuals.

3            This is somewhat of an unexpected finding in

4    light of the blood pressure differences observed in

5    the trial.  Both systolic and diastolic blood

6    pressure were decreased in the empagliflozin group

7    compared to placebo, as shown on this slide.  This

8    might be expected to reduce one's risk of a stroke

9    event.

10           The final topic that I will cover are the

11   non-cardiovascular safety findings from the

12   EMPA-REG OUTCOME trial.  Specifically, I will

13   discuss the findings for events designated as

14   adverse events of special interest, and that are

15   not already in the product label.

16           Analysis of non-cardiovascular safety was

17   based on investigator-reported adverse events,

18   review of laboratory data, and safety endpoints

19   predefined by the applicant.  The adverse reactions

20   listed in the right-hand column are serious drug-

21   related adverse reactions already featured in the

22   product label.  My talk will not focus on these.

1          I will spend the next few minutes reviewing

2     the findings related to fractures, hepatic injury,

3     malignancies, and venous embolic and thromboembolic

4     events in the EMPA-REG study.

5          Overall, fracture events were balanced

6     between the treatment groups.  However, an

7     increased risk in upper extremity fractures not

8     favoring empagliflozin was seen.  A similar

9     observation was made in another SGLT2 inhibitor

10    program.  While bone density was not assessed as

11    part of the study, the term osteoporosis was

12    reported more commonly in the empagliflozin group.

13         A signal for hepatic injury was identified

14    in the development program, and was to be followed

15    in the ongoing EMPA-REG study.  A hepatic

16    adjudication committee was tasked with determining

17    whether events of hepatic injury were causally

18    related to study drug and could represent events of

19    drug-induced liver injury.

20         Events referred for adjudication included

21    serious hepatic events and certain events based on

22    laboratory test profiles.  More events were

1    referred for adjudication with empagliflozin,

2    though nearly all events were adjudicated as

3    unlikely related to study drug.

4         A profile consistent with biochemical Hy's

5    law was reported more commonly with empagliflozin

6    than with placebo.  However, alternative etiologies

7    more likely than drug-induced liver injury were

8    identified for these events.  Overall, the findings

9    do not suggest that empagliflozin carries a

10   heightened risk for drug-induced liver injury.

11        The overall incidence of malignancy was

12   similar between treatment groups.  The applicant

13   was asked to look at some selected types of cancers

14   as events of interest, which were in balance at the

15   interim assessment.  The number of events for each

16   of these is presented here.

17        Note the 2 to 1 randomization.  The

18   incidence for these malignancies of interest were

19   generally balanced between treatment groups.  The

20   one cancer with a suggestion of increased risk was

21   pancreatic cancer.  However, the total number of

22   events is small and confounding risk factors, such

1  as obesity, diabetes, or smoking were identified in

2  review of these cases.

3  While no imbalance for venous embolic and

4  thromboembolic events has been seen with

5  empagliflozin in the original NDA review, the

6  observed increase in hemoglobin and hematocrit in

7  the development program raised some concerns.  The

8  assessment for these events was based on a review

9  of investigator-reported adverse events and

10  excluded stroke events.  No increased risk of

11  venous embolic and thromboembolic events was seen.

12  In summary, the EMPA-REG OUTCOME trial

13  suggests that empagliflozin is both non-inferior

14  and superior to placebo on the 3-point MACE

15  endpoint.  The results appear to be entirely driven

16  by the cardiovascular death component.

17  Empagliflozin was found to be non-inferior but not

18  superior for the 4-point MACE.  The review of the

19  non-cardiovascular safety was generally reassuring.

20  There are certain important factors that

21  affect our interpretability of the study results

22  and the persuasiveness of the evidence generated by

1   the study.  First, it is unclear whether this

2   single study is sufficient to support a new

3   efficacy claim.  The EMPA-REG study was designed

4   primarily as a safety trial, and the p-value for

5   superiority for 3-point MACE was 0.04.

6         The handling of silent MI in this trial was

7   not optimal, and we would like to hear your opinion

8   on this aspect of the conduct as it relates to your

9   overall assessment of the evidence.

10        Analysis of 4-point MACE and the individual

11  components of the 3-point MACE do not provide

12  persuasive evidence that the effect of

13  empagliflozin is attributable to atherosclerotic

14  cardiovascular disease risk reduction.

15        The results of the study hinge on the

16  finding of cardiovascular death.  While we

17  recognize that this is perhaps the most important

18  of all the endpoints in the composite, the high

19  proportion of non-assessable deaths in EMPA-REG

20  study may impact your interpretation of the

21  evidence.

22        With the limited information on these

1    deaths, it is difficult to know for certain whether

2    they were truly cardiovascular deaths, and what

3    mechanism might be driving the CV death result.

4              Thank you, and we look forward to your

5    discussion around these issues during this

6    afternoon's session.

7                    **Clarifying Questions to FDA**

8              DR. SMITH:  Thank you.  What we're going to

9    do now is have again clarifying questions.  We're

10   coming to discussion, but this is not the

11   discussion time.  This is really for clarification.

12   We'll focus first directing questions to the FDA,

13   and then as time allows, and then later this

14   afternoon, we'll come back to our remaining

15   clarifying questions for the sponsor.

16             Dr. Hiatt, I think you had a question?

17             DR. HIATT:  Yes.  We didn't get a chance to

18   ask this in the sponsor's presentation, but you did

19   raise an issue about silent MI, so let me pursue

20   that a little bit further.  In preparing for the

21   meeting, I sort of challenged myself to see how

22   that's handled in other cardiovascular outcome

1    trials.

2           In looking at a number of recent trials who

3    were testing more anti-thrombotic therapies, it's

4    typically included in the definition of myocardial

5    infarction.  And the CDISC definition that's most

6    commonly used would not include it as an acute MI,

7    but a significant new Q-wave that occurs after

8    randomization would be considered to be a new MI of

9    clinical significance that would be adjudicated by

10   the CEC as a myocardial infarction.

11          So the question then comes up, how do these

12   events stack up?  And if you look at again trials

13   where these are triggered as just part of the

14   clinical review and not sought after as a specific

15   case report form in a core lab, they're typically

16   few in number.  They carry clinical significance.

17   And they typically track the primary endpoint's

18   response to therapy.  But if not ascertained

19   properly, they can just add noise.

20          So the question here about ascertainment

21   bias is clearly relevant, and I think in this trial

22   went a little bit further in terms of the number of

1 the events that were captured.  It was a little

2 higher than one would expect.  So you take that

3 kind of information, and look at the MACE primary,

4 and then ask, well, had that stayed in the

5 definition, it changes the significance of the MACE

6 primary and makes it no longer significant, which

7 would kind of stop your thinking about superiority.

8    How do you view that?  I mean, you put it

9 out as a question, but it seemed that the charter

10 was changed, and I didn't see if the FDA commented

11 on that.  It wasn't clear why the CEC did that.

12 And so I'm just wondering what your thinking is

13 about how that changed the approvability around the

14 primary endpoint.

15    DR. GUETTIER:  So as Dr. Lungu stated, the

16 silent MI were a topic of confusion in the actual

17 review of this application.  And the final

18 definition that was used for analysis of silent MI

19 was purely ECG based, and that was something that

20 we had to clarify with the applicant.

21    What seemed to have happened in the trial is

22 that there was no real specification in the

1     protocol, other than for a secondary endpoint, that

2     silent MI would be looked at.  Again, we don't

3     really have, as Dr. Lungu stated -- it was never a

4     topic of discussion between the division and us

5     with regards to inclusion of silent MI in the

6     primary endpoint, but it wasn't specifically or

7     explicitly excluded from the endpoint.  The

8     protocol itself, as Dr. Lungu stated, suggested

9     that actually the applicant collected information

10    that could be used to analyze silent MI.

11          What was not clear to us is whether the CEC

12    and the CEC charter ever had knew what to do with

13    these events.  They received some silent MI events

14    by investigators because the case report form

15    actually had a checkbox for silent MI.  If the

16    checkbox was checked, it would make it to an

17    adjudication package, and an adjudication package

18    would be sent to the CEC members.

19          There was some confusion as to what to do

20    with these events based on our review of the

21    record, the CEC record.  And again, it's not really

22    clear how that was resolved, but at some point,

1   before the interim, the applicant specifically

2   excluded silent MI from the primary endpoint.

3   Again, the CEC members and the applicant can best

4   speak to this, had very specific event that they

5   had to check off after they were done with their

6   adjudication.

7          Silent MI was not one of those events.  If

8   they had received a silent MI as the outcome term,

9   they had to transform that into one of the MI

10  definitions, and that happened for some events.

11  And we asked that, for the applicant, the applicant

12  have these data.  So there were some silent MI

13  events that were captured and sent to adjudication

14  and were reviewed.

15         Again, it wasn't really ever a point of

16  discussion between us and the applicant in the

17  negotiation for this trial.  And the trial was

18  complex and we were dealing with other things,

19  including how to --

20         DR. HIATT:  Just to briefly clarify.  If

21  you're going to run a cardiovascular outcome trial

22  and you present the charter to the FDA, the sponsor

1   can decide whether silent MI is in the definition

2   or not.  Because I've looked at other trials.  It's

3   kind of variable.  It's not 100 percent.  And in

4   this case, it sounds like it wasn't a review issue.

5   Is that correct?

6        DR. GUETTIER:  I mean, that's a topic for

7   discussion that we'd like your input on, whether or

8   not these types of events should be included in all

9   cardiovascular safety trial, and that's why we pose

10   the question to you today.

11        Again, we know, at least as a

12   division -- and we have our cardiology colleagues

13   here as well who can answer -- that they're

14   difficult to assess because some people have

15   baseline ECG abnormalities and so you're going to

16   get missing data in those patients.  Unless the

17   trial pre-specifies and has specific procedures in

18   place to collect ECGs, then you might just get

19   random events.

20        Then the CEC charter has to have a

21   definition or else the CEC members are at a loss

22   and will code events to something else if they can

1   find something or will just throw out these events.

2   That's maybe something the applicant can clarify.

3          DR. SMITH:  So, Dr. Hiatt, did you -- to

4   expand on your question, it would be helpful for

5   you to ask for any more clarification at this point

6   from the sponsor or should we move on with the FDA

7   clarifications?

8          DR. HIATT:  I think that answers it.  It's a

9   discussion point for later, but I'd rather not

10  prolong that now.

11         DR. SMITH:  Okay.  Dr. Heckbert?

12         DR. HECKBERT:  Yes, Susan Heckbert.  My

13  question was really on the same topic, on silent

14  MIs.  And just as a point of clarification, on

15  slide 7 and 8 of Dr. Lungu's presentation, where

16  she's talking about silent MI, she says that in the

17  data that were available on silent MI, which was

18  not complete and was perhaps suffering from a

19  variety of different limitations, you indicated

20  that only about half of patients could be analyzed

21  for silent MI due to baseline ECG abnormalities,

22  absence of post-baseline evaluation, or intervening

1    ECG changes.

2          I just wondered, with the data that were

3    available, two questions.  Were they read finally

4    by a central ECG reading center?  There was a

5    mention that one was retained early on, but I

6    wasn't sure whether these -- what data we do have

7    were read by a central center, whether that was

8    subject to individual people at each center.

9          Then the second question was, what

10    proportion of the -- so half the patients had ECG

11    data and half of them didn't.  What proportion of

12    those was it missing because of an absence of

13    post-baseline evaluation versus pre-existing ECG

14    abnormalities or intervening ECG changes?

15          DR. LUNGU:  To answer the first question,

16    they were read by the central ECG vendor.  For the

17    second question, I think we have this information

18    in a slide.  Let me look and I'll get back to you.

19          DR. HICKS:  Good morning.  My name is Karen

20    Hicks.  I'm a medical officer in the Division of

21    Cardiovascular and Renal Products, and I'm the

22    cardiology consultant to the Division of Metabolism

1   and Endocrinology Products on the review of this

2   application.

3           Dr. Hiatt, you're correct.  There are

4   arguments for and against including silent

5   MI -- can you hear me now?  There are arguments for

6   and against including silent MI in overall

7   adjudication of non-fatal MIs in cardiovascular

8   outcome trials.  There is thought to be a

9   prognostic significance, especially in diabetic

10  patients.  And for the most part, silent MIs may

11  comprise 9 to 37 percent of non-fatal MIs in a

12  particular clinical trial, and it's thought that

13  there is a worse overall prognosis.

14          LaToya, if I could please go to background

15  slide number 8 to further address the ascertainment

16  issues.  So, EMPA-REG used an algorithm for silent

17  MI that likely did not identify all potential

18  events.  They excluded patients with right bundles,

19  left bundles, look, there are ways to evaluate

20  Q-wave myocardial infarctions even in those

21  settings.

22          I reviewed some of the silent MI data,

1    didn't have to go very far to figure out that the

2    time-to-event data were completely unreliable.  We

3    were told, and we queried this many, many times,

4    and we were told that silent MI was not adjudicated

5    in this trial.  And that's not completely true

6    because just last week, we found out that some

7    silent MI was adjudicated.

8        So here's what happened in the trial, as I

9    understand it, and perhaps the applicant can

10   clarify things a little bit further.  So silent MI

11   was included as a definition in every single

12   protocol.  And in the CEC charters, silent MI was

13   not explicitly excluded.  And in fact, it was

14   listed as one of the trigger terms to collect

15   events.  So when they were scouring through the

16   safety database, they were picking up these events.

17       My understanding, based on the response we

18   received just last week, is that the silent MIs

19   that were being identified by the investigators as

20   a trigger term -- that those events went to the CEC

21   for adjudication.

22       In most cases, they were adjudicated as MIs

1      due to PCI, MIs due to CABG, some of them weren't

2      adjudicated as events at all.  Some were thought to

3      be a heart failure event.  And my understanding

4      is -- but we should check with the

5      applicant -- that those MIs were included in the

6      overall primary endpoint results.

7           The other way that silent MIs were

8      identified was through the electrocardiographic

9      core laboratory.  And what should have happened in

10      this trial but didn't, is that if the core lab had

11      identified a Q-wave MI, that an adjudication

12      package should have been put together, everything

13      should have gone to the CEC for evaluation, and

14      then things would be good.

15           But what happened was the EKG core lab, all

16      they did was send the EKG back to the investigator

17      for sign off, and I don't think that investigator

18      had all the 12-lead electrocardiograms in front of

19      him or her.  And so that's why the time to event

20      data were not reliable.

21           So in summary, the trial used an algorithm

22      that didn't likely capture all potential events.

1    The time-to-event data were unreliable.  There was

2    reportedly no oversight by the CEC of these events.

3    Again, I think prior to study initiation, there

4    really needs to be a discussion is silent MI in or

5    is it not in, so that if it is in, then it needs to

6    be adjudicated.

7         CECs do things a little bit differently, but

8    some CECs, if it's identified by a core lab, will

9    have at least one CEC member adjudicate it.  If

10   it's something that's identified by the

11   investigator, they'll have two members of the CEC

12   evaluate it.  And lastly, a number of patients

13   lacked baseline 12-lead electrocardiograms.

14        So in summary, it's unlikely that any four

15   of these factors led to differential ascertainment.

16   Silent MI was really not well handled at all.  And

17   I know at least some of the silent MI findings are

18   unreliable.  It's not like we'd want any of that in

19   the primary endpoint anyway.  And I hope that

20   answers everyone's questions.

21        DR. HIATT:  So just to understand, all the

22   points you raised were pretty clear in reading the

material, so the lean goes in the wrong direction.

Numerically, it's unfavorable.  But it sounds like

your interpretation is that's most likely a random

result because if you include those kinds of

events, it's most likely random events, so it can

go either way.  It doesn't really mean anything.

DR. HICKS:  Yes.  I have to say that we were

concerned about the exclusion of silent MI from the

primary endpoint in amendment 3.  The timing of all

of that and the timing of other things that

happened in the trial after the CEC became

involved -- any time we see changes, there are red

flags that go up.  And unless things are really

well documented about why there are changes, we

have to be concerned about other things.  Thank

you.

DR. SMITH:  So would the sponsor want to

make any additional -- I'm really just looking for

clarification, not just carrying on.

DR. WOERLE:  Hans-Juergen Woerle.  We have

to say, we added to the confusion around the topic

silent MI with the following thing we did.  We

1  captured ECG pathological Q-waves, single ECG

2  pathological Q-waves and flagged those as silent MI

3  and reported those cases as silent MI.

4      In hindsight, that term should not have been

5  used because these were single ECG measurements

6  where we have no confirmation.  We have very little

7  information on the clinical relevance of these

8  findings.  But we added this to the statistical

9  protocol as a term, the single ECG finding as a

10  silent MI.

11      That was a secondary endpoint to clarify

12  that what we had defined in the protocol is

13  actually not part of the primary endpoint because

14  it's not an adjudicated event.  It's a single ECG

15  finding.  We clarified this in a protocol amendment

16  prior to the interim analysis.  But it was very

17  clear, when you look at the adjudication charter,

18  that there was no qualification for such events to

19  be made to the CEC member.

20      Now, Jim Januzzi adjudicated these events,

21  and he can add some clarification, which may help

22  to shed some light on this.

1         DR. JANUZZI: Thank you very much for the

2 opportunity to speak on this. This is obviously an

3 important topic, as Dr. Lungu pointed out in a very

4 nice presentation. Silent myocardial infarction is

5 an important topic. Dr. Hiatt, you made this clear

6 as well. And as Dr. Hicks said, there are

7 substantial challenges to recognition and actually

8 how to adjudicate these in clinical trials.

9        So while it is clinically relevant, it's

10 challenging to recognize and adjudicate. And

11 relevant to this, the current guidance from

12 ACC/AHA, Dr. Hicks was an author, is actually well

13 silent to the definition of silent MI in clinical

14 trials' definitions.

15        When considered as an endpoint in clinical

16 trials, silent MI, the standard approach has

17 traditionally relied, as has been said, on a

18 baseline electrocardiogram, then showing a change,

19 which is then stable on subsequent measurements.

20 So it requires serial ECG measurement in order to

21 demonstrate stability of the finding.

22        This in part has to do with the fact that

1    the changes consistent with MI are evanescent.

2    They may be non-specific and may not be stable over

3    time.  Therefore, single tracing should not, by any

4    means, be used to make the conclusive diagnosis of

5    a myocardial infarction in the absence of clinical

6    signs, symptoms or other data.  As a consequence,

7    most CVOTs do not include silent MI.

8         May I have slide CV-243, please?  That would

9    be slide 1 up.  Just an example of the current

10   cardiovascular outcomes trials looking in diabetes

11   since 2008 as well as some of the older, just

12   illustrating the heterogeneity with respect to

13   inclusion or not of silent myocardial infarction.

14        Now, relevant to EMPA-REG -- and this slide

15   can be taken down, thank you.  Relevant to EMPA-REG

16   OUTCOME the term silent MI, as Dr. Woerle just

17   said, is somewhat inaccurate, actually, and

18   somewhat of an unfortunate term that was used.

19        From the CEC's point of view -- and I'd

20   emphasize that if an investigator felt a patient

21   had suffered a myocardial infarction, silent or

22   otherwise, they could send the information to the

1    CEC for adjudication.  So, in point of fact, if

2    triggered, MI would have been evaluated for on our

3    level and the CEC, so silent MI technically was not

4    excluded from consideration.

5         What was triggered here were

6    electrocardiograms that were flagged as showing a

7    possibly new abnormality.  And in these 53 tracings

8    that Dr. Lungu analyzed in her sensitivity

9    analysis, of those 53 flagged

10   electrocardiograms -- I choose that terminology

11   rather than calling them silent MI -- the site was

12   actually queried by the central ECG lab, core lab,

13   reviewed by the investigator and their

14   cardiovascular consultant.

15        Only 3 were sent to the clinical endpoints

16   adjudication committee for review.  Of those

17   patients, only 1 was adjudicated as having

18   hospitalized heart failure, and none were

19   adjudicated as having a myocardial infarction.

20        One last point I think that would be helpful

21   for reassurance -- may I have slide 1 up,

22   please -- is relevant to the outcomes of the

1   patients that had these flagged ECGs, these 53

2   patients.  We see, on the top line, the patients

3   that suffered subsequent mortality and then

4   adjudicated cardiovascular death.  The flagged ECGs

5   are in the right column.  We see a substantially

6   lower mortality rate overall compared to patients

7   with adjudicated non-fatal MI using standard

8   criteria.

9       Of the CV deaths, there were two, one was

10   sudden cardiac death and the other was death due to

11   pulmonary thromboembolism.  So at least this

12   provides some information on the CEC level at least

13   relative to these specific patients, more specific

14   data from the sponsor.  I'll defer.

15       DR. SMITH:  All right.  Dr. Konstam, do you

16   have a follow-up question on the same topic?

17       DR. KONSTAM:  Yes, I do.  So, Jim, just to

18   kind of nail down a couple of things.  Okay.  The

19   ones that you did adjudicate that were sent in from

20   the investigators as silent MIs, what happened to

21   those patients?  Are they in the final results or

22   not?

1      DR. JANUZZI:  So they were as you saw in

2   that last slide I showed.  So yes, in fact, if a

3   patient was sent in with a trigger term, silent MI,

4   we would look at the event that the investigator

5   was triggering.  And as I said, and as Dr. Hicks

6   indicated, in some cases they were MIs related to

7   PCI, they were CABG MIs.  So they were considered,

8   sure.

9      DR. KONSTAM:  So if you considered them MIs,

10  they were counted as MIs.

11     DR. JANUZZI:  Yes, exactly.

12     DR. KONSTAM:  Okay.  So this relates to my

13  next question.  So let me just say, I can go either

14  way with inclusion or exclusion.  What's more

15  concerning is changes that occur from prespecified

16  terms, and in practice during the course of the

17  trial.  So at some point in time -- we hear it was

18  before the interim analysis -- the sponsor

19  determined that silent MIs would not be included.

20     Now, I want to understand a few things about

21  that.  Why did you do that at that point in time?

22  Who participated in that decision?  And how did you

1   deal with the fact that they had already included

2   silent MIs, as long as they came from the

3   investigator?

4          DR. WOERLE:  To clarify, we used an

5   unfortunate term.  What we wanted to clarify in the

6   protocol that single ECG abnormalities, not being

7   confirmed by the adjudication committee as an MI,

8   should not be included.  When you look -- and I

9   would need Jim for confirmation here -- when you

10   look at the CEC charter, the initial CEC charter

11   did not have the term silent MI, but all pathologic

12   clinically relevant MIs were included in the

13   analysis.  But please, Jim, would you comment?

14          DR. JANUZZI:  I can keep it simple on the

15   answer.  Any case that was sent to us that looked

16   like an MI was adjudicated as an MI, and was

17   therefore included.

18          DR. KONSTAM:  Even if the investigator

19   indicated silent MI?

20          DR. JANUZZI:  That's correct.  And that

21   speaks, to some extent, to the investigator at the

22   sites accuracy for the event itself.

1          DR. KONSTAM:  What is it that made you make

2     that decision at that point in time?  Was it based

3     on what?

4          DR. WOERLE:  Can we have the slide on the

5     initial protocol?  Slide 1 up, please?  That's the

6     definition of the initial protocol.  It states

7     primary event comprises adjudicated composite of CV

8     death, non-fatal MI, and non-fatal stroke.  To the

9     adjudication committee, any potential trigger which

10    would qualify for these endpoints had been sent.

11         Now, from this protocol amendment, from this

12    protocol, it's not entirely clear whether silent MI

13    is included or not.  And type 4 and type 5 MIs,

14    which can be considered as MI, are actually

15    included.  Now, to clarify this, we have to have a

16    look at the CEC charter.

17         Slide 3 up, please.  That's an extract of

18    the CEC charter.  And here in the CEC charter, the

19    adjudication committee has the opportunity to

20    potentially trigger the following events,

21    hard-outcome events.  And as you can see, the term

22    silent MI, what we defined as a single ECG

1   abnormality which was not confirmed by subsequent

2   ECG and additional information, which then had been

3   adjudicated as an MI, are not mentioned here.

4   To clarify this, we in the first protocol

5   amendment, made the clarification that silent MI

6   are excluded from the primary endpoint.  It would

7   have been hindsight, much clearer to state --

8   DR. KONSTAM:  But not silent MIs that were

9   identified by the investigator?  Is that what you

10  said in the amendment?  Did the amendment say

11  silent MIs would be excluded unless they are

12  identified by the investigator and sent into the

13  adjudicating committee?

14  DR. WOERLE:  Dr. Broedl, would you like to

15  comment?

16  DR. BROEDL:  Uli Broedl, Medicine.  So to

17  address your question, what did we state in the

18  protocol, we unfortunately stated simply excluding

19  silent MI.  But I want to make it very clear -- and

20  I would like to have the process slide -- how the

21  adjudication went.  What Dr. Lungu nicely presented

22  was what happens if you add 53 flagged ECGs, which,

1    as Dr. Hicks pointed out, mixed with the primary

2    endpoint.

3         What happened in terms of silent MI analysis

4    is the following.  Can I please have the silent MI

5    assessment?  If an investigator considered

6    something like a silent MI as an adverse event,

7    this adverse event had to be entered into remote

8    data capturing system.

9         The vendor then assessed whether the term

10   that was reported matches a trigger list of terms

11   and be used on the SMQ, ischemic heart disease.  We

12   used cardiac failure, and we used Torsade de

13   points.  SMQ, the SMQ ischemic heart disease,

14   included the trigger term, silent MI.

15        However, the CEC charter, which you can find

16   in our briefing book, clearly specified for type 1

17   and type 2 MI, which were by far the most frequent

18   MIs in this trial, that patients have to have

19   symptoms, in addition to one of the following

20   criteria, including biomarker, ECG changes, or

21   imaging, and this is depicted in slide 1.  Up,

22   please.

1          So in essence, the vendor checked whether a

2     trigger term was reported by the investigator.  The

3     trigger terms included, for instance angina

4     pectoris, but also silent MI.  The CEC panel, based

5     on the criteria that you can find and that I

6     alluded to, assessed whether this is enough

7     evidence of a cardiac event in a clinical setting,

8     but only had the opportunity to report those

9     non-fatal cardiac events that are listed here,

10     non-fatal MI, hospitalization for unstable angina,

11     coronary revascularization, stent thrombosis, and

12     heart failure hospitalization.  The panel did not

13     have the opportunity to specifically vote for

14     silent MI.

15          DR. HICKS:  May I clarify?

16          DR. SMITH:  Yes.

17          DR. HICKS:  So, in response to Dr. Januzzi's

18     comments, I just wanted to clarify that we actually

19     do have a definition for silent MI.  It's called

20     prior myocardial infarction.  And the

21     electrocardiographic criteria for prior MI are

22     exactly the same as silent MI.  And this is not

1    only in our data standards paper.  It's also in our

2    draft definitions dated August 2014.

3            By the way, these definitions are in each

4    CEC charter.  And there were a lot of charters and

5    a lot of changes in the charters that went on

6    during the course of the study.  Thank you.

7            DR. SMITH:  Thanks.  I'm going to move us

8    along.  We may return to this point later on.

9            Dr. Schambelan, you had a question?

10           DR. SCHAMBELAN:  My question is long.

11           DR. SMITH:  Dr. Neaton?

12           DR. NEATON:  My question is simpler.  So in

13   the FDA briefing document, on page 75, where

14   there's a description of some of the missing data,

15   there's reference to 74 subjects with positive

16   MACE, non-fatal events that could not be assessed

17   by the clinical events committee.  Could you shed

18   some light on what you're referring to there and

19   the significance of that?

20           DR. GUETTIER:  That's Dr. Hicks's --

21           DR. NEATON:  I believe that was Dr. Hicks's

22   document, yes.

1          DR. HICKS:  Yes, thank you.  Actually, that

2     was another information request we had made to the

3     applicant, and they had prepared that data.  So

4     there were, in addition to the 200 or so patients

5     who were missing MACE for a period of time, there

6     were also approximately 70 patients who had

7     potential MACE events.  Not all of them, but some

8     of those 70 had potential MACE events and Jennifer

9     Clark has done a number of sensitivity analyses

10    looking at that.

11         DR. NEATON:  When you say a potential MACE

12    event, there was some information, documentation

13    provided that they were ruled out as a MACE event?

14         DR. HICKS:  No.  Actually, the CEC was

15    unable to adjudicate these particular cases.  So

16    they were potential events, but because the data

17    were incomplete, they couldn't finalize the

18    adjudication diagnosis.

19         DR. SMITH:  What I would like to as -- there

20    are more questions.  If there are any committee

21    members that have questions that may lead to some

22    preparation of some data that might be brought to

1　us later this afternoon, I'd like to prioritize

2　that.  Anybody have a question in that regard?  Dr.

3　Wilson?

4　　　　　DR. WILSON:  So I believe in the product

5　label, it says contraindication for an eGFR less

6　than 45.  And I'm not able, from the materials I've

7　heard so far, to figure out what happened to those

8　people and how many people were in that group in

9　the trials.

10　　　　　There's a creatinine doubling and eGFR less

11　than 45, but in fact the label says eGFR less than

12　45, you're not to prescribe the drug.  So I think

13　that would be worth knowing, that safety data, and

14　whether it affects -- and what happened to those

15　people?  Did they stop using the drug?

16　　　　　DR. SMITH:  Yes.  Do you have the data now

17　or would you like to pull that together for this

18　afternoon?

19　　　　　DR. WOERLE:  We can put this up for you.

20　Let's remember, the trial was started, part of the

21　phase 3 program, when it was not clear what

22　limitation in terms of renal function we would see.

1    We specifically looked into patients who have eGFR

2    less than 60 but also less than 45.  And my

3    colleague from drug safety, Gabriel Kim, looked

4    into this and will walk you through what we saw.

5            DR. KIM:  Gabriel Kim, Boehringer Ingelheim.

6    We have specifically analyzed patients with CKD

7    stage 3b.  Overall, in terms of the general safety

8    findings, it was consistent what we observed for

9    the overall population.  In addition to this, we

10   also looked at the MACE endpoint and cardiovascular

11   endpoints, which also suggested a similar effect

12   within this population.

13           Finally, in terms of a renal endpoint that

14   we looked at, there was also shown a similar effect

15   in terms of renal safety and endpoints.

16           DR. WILSON:  Just as a follow-up, the people

17   continued taking medication whether -- they weren't

18   pulled out.  They weren't censored?  Just so I

19   know.

20           DR. KIM:  So, to answer your question, they

21   were not instructed to discontinue medication once

22   they have reached a CKD 3b eGFR category.

1          DR. SMITH:  Thanks.  We do have some more

2     questions.  I apologize to people who haven't been

3     able to ask their questions.  We will come back to

4     those, but by the clock we really need to break for

5     lunch at this point.

6          So, we're going to take a lunch break.

7     We're going to come back here, we're starting a

8     little late, so we'll come back at 10 minutes past

9     1:00.  And please take any personal belongings you

10    may want with you at this time.  Committee members,

11    please remember there should be no discussion of

12    the meeting during lunch, amongst yourselves, with

13    the press, or with any member of the audience.

14    Thank you.

15          (Whereupon, at 12:20 p.m., a lunch recess

16    was taken.)

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

2              (1:22 p.m.)

3           **Open Public Hearing**

4         DR. SMITH:  I encourage people to take their

5    seats so we can get started here.  We're still

6    missing a few and we'll wait a minute or two.

7    Okay.  I think we'll start the afternoon part of

8    today's work.

9         Both the Food and Drug Administration, the

10   FDA, and the public believe in a transparent

11   process for information gathering and decision

12   making.  To ensure such transparency at the open

13   public hearing session, which is what we're going

14   to have scheduled next, the FDA believes that it's

15   important to understand the context of an

16   individual's presentation.

17        For this reason, FDA encourages you, the

18   open public hearing speaker, at the beginning of

19   your written or oral statement, to advise the

20   committee of any financial relationship that you

21   may have with the sponsor, its product, and if

22   known, its direct competitors.  For example, this

1 financial information may include the sponsor's

2 payment of your travel, lodging, or other expenses

3 in connection with your attendance at the meeting.

4 Likewise, FDA encourages you, at the

5 beginning of your statement, to advise the

6 committee if you do not have any such financial

7 relationships. If you choose not to address this

8 issue of financial relationships at the beginning

9 of your statement, it will not preclude you from

10 speaking.

11 The FDA and this committee place great

12 importance in the open public hearing process. The

13 insights and comments provided can help the agency

14 and this committee in their consideration of the

15 issues before them.

16 That said, in many instances and for many

17 topics, there will be a variety of opinions. One

18 of our goals today is for this open public hearing

19 to be conducted in a fair and open way, where every

20 participant is listened to carefully and treated

21 with dignity and courtesy. Therefore, please speak

22 only when recognized by the chairperson. Thanks

1    for your cooperation.

2         At this point, will speaker number 1 please

3    step up to the podium and introduce yourself?

4    Please state your name and any organization you are

5    representing for the record.

6         DR. GRUNBERGER:  Thank you, Mr. Chairman.

7    It's always fun to be the first speaker after

8    lunch.  I'm George Grunberger, and I represent the

9    American Association of Clinical Endocrinologists.

10    The sponsor played no role in financing my trip

11    here.

12         The American Association of Clinical

13    Endocrinologists is the largest organization of

14    clinical endocrinologists in the world, which

15    comprises over 7,000 members from 97 countries.

16    The mission statement of AACE is that it's a

17    professional community of physicians specializing

18    in endocrinology, diabetes, and metabolism,

19    committed to enhancing the ability of its members

20    to provide the highest quality of patient care.

21         I don't have to emphasize to this audience

22    the burdens of type 2 diabetes, whether financial

1   or in terms of suffering, the complications.  As we

2   know, even today, it remains the leading cause of

3   blindness in adults, leading cause of kidney

4   failure, the leading cause of lower limb

5   amputations.  Relevant to this meeting, the

6   patients with diabetes are much more likely to have

7   hypertension, cardiovascular disease, stroke, and

8   other complications.

9       We know that diabetes doubles the risk of

10  vascular events, whether it's coronary heart

11  disease, cerebrovascular disease, cardiovascular

12  deaths.  We know that diabetes confers the highest

13  lifetime risk of coronary heart disease of any

14  single risk factor.  And we've seen that diabetes

15  is associated with significant loss of life years,

16  and the vascular deaths contribute the majority of

17  this life lost.

18      We are here because the 2008 FDA guidance

19  for diabetes drugs was designed to assure

20  cardiovascular safety.  It was not designed to

21  demonstrate benefit.  So all trials we have

22  reported out to date show that safety until we have

EMPA-REG OUTCOME, which sort of is the reason we are here for today.

We've seen that in the primary outcome, the 3-point MACE, there was a significant 14 percent reduction of 3-point MACE, which was driven largely by the cardiovascular death with its 38 percent reduction. And also hospitalization for heart failure was significantly improved in patients on empagliflozin. To make it more interesting, only one of this 3-point MACE was significantly affected. It was a cardiovascular death with no significant improvement for patients on empagliflozin when it came to non-fatal MI or stroke.

So every day, after September 17, 2015, I've been asked three questions. Is this is a class effect? Should all patients with type 2 diabetes be put on SGLT2 inhibitor or empagliflozin specifically? And when will AACE, in view of a positive important outcome in our leader results, change its diabetes algorithm?

Well, let me start with the last one.

1    That's easy.  AACE does not have to change

2    anything.  GLP-1 receptor agonists and SGLT2

3    inhibitors have already been the top two choices in

4    our diabetes algorithm initially or right after

5    metformin for the last three years.

6         This is a 2016 version of AACE comprehensive

7    diabetes algorithm, which you can see whether for

8    monotherapy, dual therapy, or triple therapy, GLP

9    receptor agonist and SGLT2 inhibitors have been

10   chosen as the two leading categories in trying to

11   control glycemia in patient type 2 diabetes.

12        We do have obviously very strict

13   recommendations when it comes to management of

14   dyslipidemia and hypertension also for patients

15   with type 2 diabetes because we believe every

16   patient with this condition is at high and very

17   high risk for cardiovascular complications.

18        If you look on the next slide and the 2016

19   diabetes algorithm, they already included when we

20   talked about the profiles in diabetic medications a

21   possible benefit for SGLT2 inhibitors for

22   congestive heart failure, but we believe there is

1    no effect on progression of atherosclerotic

2    cardiovascular disease.  So we recognize possible

3    outcomes from the EMPA-REG study.

4          So is this a class effect?  Well, who knows?

5    As you know, the canagliflozin, empagliflozin

6    studies will not be out for the next couple of

7    years.  And they have recruited somewhat different

8    patient populations, so it might be difficult to

9    compare those results.  Again, remember that the

10    key inclusion criteria for EMPA-REG study included

11    not only long-term uncontrolled type 2 diabetes,

12    but established cardiovascular disease.

13          So should every patient with type 2 diabetes

14    today be placed on empagliflozin or at least a

15    SGLT2 inhibitor?  We believe that would be

16    premature because we have only one study and only

17    one component of the primary endpoint, which was

18    significantly positive.

19          So at this point we can recommend that only

20    patients who fit the inclusion criteria of EMPA-REG

21    OUTCOME should be considered, and for others let's

22    wait for results of studies and real-world

1    postmarketing data in patients with type 2 diabetes

2    who did not meet the specific inclusion criteria

3    for EMPA-REG OUTCOME study.

4         So in closing, the American Association of

5    Clinical Endocrinologists does not advocate for

6    approval or indication for any specific drug.

7    However, we recognize there is a great need for new

8    drugs to help manage the ever-increasing burden of

9    type 2 diabetes.  And we certainly need more

10   effective and safer medications to improve

11   metabolic control of our patients without the risk

12   of hypoglycemic weight gain, and now hopefully with

13   cardiovascular benefit.  Thank you.

14        DR. SMITH:  Thank you.  Will speaker

15   number 2 now please step up to the podium and

16   introduce yourself?  Please state your name and any

17   organization you may be representing for the

18   record.

19        MS. GAO:  Good afternoon.  My name is

20   Helen Gao, and I'm here today representing the

21   diaTribe Foundation, a diabetes patient advocacy

22   non-profit based out of San Francisco.  Donors to

1   the diaTribe Foundation include the Helmsley

2   Charitable Trust and many others, including today's

3   sponsor.  By way of disclosures, I also work for

4   Close Concerns, a healthcare information company

5   focused on diabetes and obesity.  My colleague,

6   Emily Reiger, will review Close Concerns'

7   disclosures later this afternoon.

8           Today, I'd like to speak about an update

9   indication reflecting a cardiovascular benefit for

10  JARDIANCE in high-risk patients and what that could

11  mean for patients and physicians.  I was at the

12  presentation of the full results from EMPA-REG

13  OUTCOME at EASD last September, and vividly

14  remember the air of excitement and wonder as a risk

15  reduction for each endpoint was revealed to

16  thunderous applause.  It was truly a historic

17  moment.

18          Coming out of the session, I was surprised

19  and disappointed to see that the results weren't

20  front page news in the mainstream press.  I

21  wondered how the average patient or the average

22  primary care physician, who has so many demands

1   beyond diabetes, will learn of these unprecedented

2   results.

3        An updated indication clearly stating that

4   JARDIANCE can reduce mortality in high-risk

5   patients through the reduction of cardiovascular

6   death and heart failure would go far in publicizing

7   with historic and clinically meaningful benefit.  A

8   38 percent relative risk reduction in

9   cardiovascular death is huge, and patients and

10  healthcare professionals need to know about it.

11       Furthermore, many patients with type 2

12  diabetes might not even fully understand the link

13  between diabetes and increased cardiovascular risk.

14  If you put clear language about cardiovascular

15  outcomes on the label of a diabetes drug, you

16  increase the chances of a conversation about that

17  risk between doctors and patients.

18       For the physicians and patients who are

19  already aware of that cardiovascular risk but have

20  not been able to mitigate it as trial after trial

21  showed little impact on cardiovascular outcomes,

22  JARDIANCE offers a new hope.  It could mean a

1     longer, healthier life with less time spent in

2     hospitals.

3           That's a big win for patients, and a big win

4     for the morale of healthcare professionals.  For

5     too long, those in the diabetes field have felt, in

6     the words of the musical Hamilton, outgunned,

7     outmanned, outnumbered, and out-planned.  I

8     sincerely hope that the committee will vote today

9     in favor of letting healthcare professionals and

10     patients know that they have one more tool in the

11     fight against diabetes.  Thank you.

12           DR. SMITH:  Thank you.  Will speaker

13     number 3 now please step up to the podium and

14     introduce yourself?  Please state your name and any

15     organization you are representing for the record.

16           MS. REIGER:  Good afternoon, and thank you

17     for the opportunity to speak today.  My name is

18     Emily Reiger and I am here representing Close

19     Concerns, a healthcare information company that

20     aims to improve patient outcomes by making people

21     smarter about diabetes and obesity.  As far as

22     disclosures go, today's sponsor is one of almost

1   300 organizations that subscribe to our fee-based

2   newsletter, Closer Look.

3         Today, I'd like to take a step back and

4   offer a few big picture thoughts on what JARDIANCE

5   and especially the benefits demonstrated in

6   EMPA-REG OUTCOME mean for patients with diabetes

7   and their healthcare providers.

8         Thanks to the FDA's recommendation that

9   these major outcomes trials be done, we now have

10  valuable information on JARDIANCE that can help

11  healthcare providers as they choose among the many

12  different options for patients with type 2

13  diabetes.  We know this trial required a

14  substantial investment of time and money, and we

15  want to ensure that the diabetes community can gain

16  as much value as possible from that investment.

17        People with diabetes want to live long and

18  they want to live well.  Few people expected that

19  findings of lower cardiovascular risk would emerge

20  so clearly in this trial, even if for only a small

21  group of patients.  Given the staggering prevalence

22  and cost of diabetes and its complications, a

1   product that reduces the risk of a negative outcome

2   for even a small percentage of patients could have

3   a significant impact on the healthcare system.

4           We understand that any label update will

5   need to include statements about the limitations of

6   the data and how much it can be generalized.  And

7   we'll leave it to the experts to debate the more

8   technical questions related to trial design.

9           However, we think it's important for today's

10  busy healthcare providers to have the opportunity

11  speak broadly with patients at high risk of

12  cardiovascular disease about the potential benefits

13  of this medication.

14          We would love to see increased awareness

15  among people with diabetes about the risks of

16  cardiovascular disease, and we think that including

17  this data on the label can be an important

18  component of that effort.  So thank you again for

19  the opportunity to speak and for your consideration

20  of these matters.

21          **Clarifying Questions (continued)**

22          DR. SMITH:  Thank you.  The open public

1    hearing portion of this meeting has now concluded

2    and we will no longer take comments from the

3    audience.  And what we're going to do first is to

4    resume the opportunity to ask any more clarifying

5    questions from the committee.  And before that, the

6    sponsor has asked if they could briefly provide

7    some additional clarifying points on questions that

8    were raised this morning.  So we'll go to that step

9    now.

10          Dr. Woerle?

11          DR. WOERLE:  More patients, and we weren't

12   sure if we delivered you the right answer.  These

13   74 non-fatal adjudicated events, which were not

14   assessable, these patients were included in the

15   analysis, but the events were not counted as

16   outcome events.  I hope this helps to clarify this

17   point.

18          The second point, we wanted to make clear on

19   the topic of silent MI.  We conducted routine ECG

20   measurements and this should be seen as casting a

21   net most sensitive to get as many information as

22   possible.  However, only events who have been

1   raised by the investigator have been reported to

2   the adjudication committee.  And of course all

3   events who have been reported to the adjudication

4   committee have been adjudicated as outcome events

5   or not.

6        The third point I wanted to make on presumed

7   cardiovascular death.  While the number appears

8   somewhat high, I wanted to remind the committee

9   that in a patient population with established

10  cardiovascular disease where you can assume that

11  this was not a non-cardiovascular event, it is

12  reasonable to conclude that these patients should

13  be included as presumed cardiovascular death and

14  actually that this is standard in most of the

15  cardiovascular outcome trials.

16       DR. SMITH:  Okay.  Thank you.  So, back to

17  questions.  And I'm going to start with people who

18  got left out earlier for schedule reasons.  So,

19  Dr. Everett, we'll lead off with you.

20       DR. EVERETT:  Thank you.  Actually, my

21  question pertains to the last comment that the

22  sponsor just made, and also maybe applies to

1   something that the FDA mentioned earlier.  In

2   particular, I think this idea that the patients who

3   had a presumed and non-assessable death, that was

4   then presumed to be cardiovascular in etiology, I

5   tend to agree with you that it might be a

6   reasonable presumption that those are

7   cardiovascular deaths.

8        So my question to the sponsor is, why were

9   those deaths not included in the primary endpoint

10   as initially specified, either in the protocol or,

11   as I understand it, until the statistical analysis

12   plan was modified on May 21, 2015, after the trial

13   was closed, last patient, last visit was completed?

14        DR. WOERLE:  Please let me clarify.  In the

15   adjudication charter issued in 2010, it was already

16   clearly stated that presumed cardiovascular death

17   events would be counted as part of the primary

18   endpoint.

19        DR. EVERETT:  So where's the confusion that

20   this was not part of the primary endpoint until

21   2015 then?  Or sorry, yes, May 21, 2015.  Why does

22   there seem to be a discrepancy about that?

1          DR. WOERLE:  I'm not entirely clear where

2     this confusion comes from.  I can show you the

3     adjudication charter where it clearly states that

4     presumed cardiovascular death would be part of the

5     primary endpoint.

6          DR. EVERETT:  Is it not in the statistical

7     analysis plan?  I mean, that's what the FDA's

8     documentation would appear to say.  And the reason

9     why I mention this, of course, is because when you

10    remove them from the primary endpoint, there are

11    changes in the level of significance as seen on one

12    of the FDA slides, which I can find for you here in

13    a moment.  Slide number 12.

14          DR. WOERLE:  So allow me to clarify.  From

15    the very beginning the CEC charter -- and we have

16    documented this -- in the initial version of the

17    CEC charter stated that CV death includes presumed

18    CV death.  That was in 2010.  This was added then

19    in the TSOP for clarification to align with the CEC

20    charter.  But it was always the intention of the

21    sponsor, at any point in time, to include presumed

22    CV death.

1          DR. EVERETT:  Does that answer the FDA's

2     concerns about this issue, about how the presumed

3     cardiovascular deaths were not included and then

4     were included?

5          DR. GUETTIER:  So we are in agreement with

6     the sponsor that, in the CEC charter, the CEC

7     charter from the beginning, at least the nine

8     versions that we've reviewed, stated that

9     non-assessable deaths would be counted as CV

10    deaths.  I believe the CEC form that was used for

11    adjudication included CV death as a criteria for

12    deaths.

13         The statistical analysis plan change was a

14    specification that it would not be included, and

15    that was done late.  But we have no basis for

16    thinking that whatever happened in the CEC charter

17    wasn't going to be followed.  I mean, at least

18    that's the division's perspective.  There might be

19    some difference of opinion within the agency.

20         DR. HICKS:  Thank you.  This is Karen Hicks.

21    I'm a medical officer in the Division of

22    Cardiovascular and Renal Products, and I'm the

1   cardiology consultant to the Division of Metabolism

2   and Endocrinology Products for this application.

3         I can't believe I'm actually helping the

4   applicant here, but the CEC charter actually did

5   have a line in one of the first paragraphs.  And so

6   I can attest to that.  But I'd like to carry this a

7   little bit further because it was never

8   prespecified in any of the protocols.  And this

9   change right before the end of the trial

10  unblinding, it was just kind of strange to see in

11  the statistical analysis plan.

12        So if I could, LaToya, may I please have

13  slide number 10 up?  Here's what our FDA draft

14  definitions paper says about undetermined deaths.

15  And as you know, undetermined deaths were presumed

16  to be cardiovascular deaths in this trial.

17        There are a couple of caveats.  So in

18  general, we believe that most deaths can be

19  classifiable as either cardiovascular or

20  non-cardiovascular.  But the use of this category

21  of death, undetermined cause of death, should be

22  discouraged, and should apply to few patients in

1    well-run clinical trials.

2          124 patients with undetermined deaths is not

3    a small number of patients.  That's actually a

4    large number of patients.  And we go on to

5    state -- slide number 11 please -- that it's a

6    common analytic approach for cause-of-death

7    analyses.  And the caveat is that the approach

8    should be prespecified, and we actually encourage

9    that.  It is not only in the CEC charter, but also

10    in the protocols and also in any of the other trial

11    documentation and statistical analysis plan.

12          So moving forward to slide number 12,

13    please.  So in summary, it's something that should

14    be prespecified, but the caveat is, is that the

15    number of undetermined deaths should be few.  And

16    when we see this many undetermined deaths, we know

17    that there's missing data.  I read the CEC minutes.

18    The CEC members were marveling at how much data

19    were missing for these undetermined deaths, and

20    they kept requesting further information.

21          If you look at these cases, these deaths are

22    completely uninterpretable, and they could be

1   non-cardiovascular deaths.  They could be

2   cardiovascular deaths, and there could be many

3   possible etiologies, cardiovascular death due to

4   myocardial infarction, due to stroke, due to heart

5   failure, due to sudden death, but it was really a

6   mixed bag.  And I think, had there been more

7   rigorous follow-up of this death information, that

8   we may have a better idea about the mechanism

9   behind cardiovascular death in this trial.

10   I think the take-home message here is, all

11   of that said, if you do an extreme analysis and

12   exclude all these undetermined deaths from the

13   analysis, the effect on CV death is still robust.

14   Thank you.

15   DR. SMITH:  Thank you.  Dr. Rosenberg, you'd

16   had a question hours ago this morning, and I've not

17   forgotten you if you still have a question.

18   DR. ROSENBERG:  Well, they have accumulated

19   since this morning, of course.  If you will allow

20   me, I will take a little more time.  I try with one

21   not-simple question, but one question and then go

22   back to the rationale and the background behind

1    that simple question.

2         I would like to ask the sponsor, given all

3    the problems in collecting deaths and documenting

4    events, as Karen just outlined, why not come back

5    to a little bit of sanity here and a little bit of

6    simplicity about what clinical trials used to be

7    about, improving patient survival?  So why not

8    propose an indication for overall survival in this

9    trial as you obviously had the power for it?

10        So now let's go back to what's behind this.

11   The undetermined cause of deaths, and I think Karen

12   just brought back the issue and it's still strong

13   here.  But it brings back to fact that it's very

14   hard to classify deaths, but still, as has been

15   said, it's really too high a number.  And then

16   there's the problem of the silent MI.  And even the

17   best expert in the world, like Marc Pfeffer, just

18   really don't know how to classify silent MI, so

19   that should that even be included there?

20        I'm not sure we need to spend hours

21   discussing silent MI that shouldn't even be

22   considered probably in this type of trial if you

1    don't have a prespecified process, very carefully

2    designed case report form, to collect the

3    information systematically.  And then maybe the CEC

4    can do a decent job and even there it's very hard.

5         Then finally, the adjudication process -- I

6    think, at some point, we need to revise what we are

7    doing here in terms of adjudication.  The Cochrane

8    just published a meta-analysis of 47 studies of

9    277 -- 375,000 patients comparing adjudication

10   versus no adjudication versus investigator-reported

11   deaths.

12        There's absolutely no difference, except, as

13   a caveat, maybe when the investigators are

14   unblinded.  And here, we can assume that probably

15   most of them were unblinded even if it was

16   supposedly a double-blinded study, but they knew

17   what the glycemia was, if it was going down or not,

18   so just a little caveat.

19        But I think we have to question the value of

20   adjudication here.  Karen asked you and probably

21   won't answer how many millions you spent on

22   adjudication that may be used to form better

1    research here.  And I think the FDA leadership has

2    a very strong idea there, so we'll move on and

3    maybe we'll get -- the FDA will get away with

4    adjudication in most trials.  So maybe you can

5    answer the question.

6         DR. WOERLE:  Okay.  CO-72, please.  Slide 2

7    please up.  This is the finding on all-cause

8    mortality.  Our interpretation was, since CV death

9    had a hazard ratio of 0.62, with a highly

10   significant p-value, whereas non-CV death had a

11   hazard ratio of 0.84, but not significant, that the

12   benefits we see in overall mortality are largely

13   driven by CV death.

14        It's also our understanding that, very

15   unfrequently, overall mortality indications are

16   granted and we focused on the most relevant finding

17   of the EMPA-REG OUTCOME trial, which was the

18   finding on CV death.

19        I could not agree with you more, and

20   probably Jim Januzzi will say the same, on the

21   difficulties of adjudicating outcome events, in

22   particular causes of death.  I wanted to point out

1    that we had an extremely rigorous process.  The

2    adjudication committee, whenever they felt they

3    would not have enough information to determine the

4    cause of death, asked the sponsor to reach out to

5    the investigator.  We had three attempts to get as

6    many information back to the adjudication committee

7    as possible.

8          Then I would like to add one point on

9    presumed CV death.  If the committee is concerned

10    about the finding on presumed CV death and exclude

11    that from the CV death findings, since these people

12    have died, there is no doubt, it would be logical

13    then to count them as non-cardiovascular death, and

14    I would like to show what happens then.  That's

15    slide 2 up please.

16          Obviously, the finding on all-cause

17    mortality remains highly significant.  CV death

18    remains highly significant with a hazard ratio of

19    0.59.  But now non-CV death becomes significant,

20    which gives you an idea on the robustness of the

21    finding we have observed in the EMPA-REG OUTCOME

22    trial.

1          The last point you made on the CEC charter,

2    I'm not sure.  You asked something on the CEC

3    charter.  Have I clarified or commented on what you

4    wanted to know there?

5          DR. ROSENBERG:  Well, I don't think you can

6    answer the question.  Whatever the charter says

7    about classification, if you haven't collected the

8    information, there's no way you get something

9    valuable.

10          DR. SMITH:  Okay.  Dr. Wilson, you had had a

11    question much earlier.

12          (No response.)

13          DR. SMITH:  Dr. Hiatt, you had had one much

14    earlier resolved.

15          (No response.)

16          DR. SMITH:  Dr. Proschan, also much earlier?

17    I'm aware of that.

18          DR. PROSCHAN:  Right.  No.  I was interested

19    in the stroke analyses.  There was an increase in

20    stroke, and I absolutely agree with the sponsor

21    that looking at overall stroke, fatal and

22    non-fatal, is what we should be doing.  It does not

1    make sense to look at non-fatal stroke if you have

2    to censor fatal stroke.  That just makes no sense.

3         But there was that stroke disadvantage

4    despite an advantage in terms of the blood

5    pressure.  And I'm just wondering has anyone done

6    any kind of analyses where you look at differences

7    in stroke.  And I know this is a dangerous thing to

8    do, but trying to adjust for post-randomization

9    blood pressure, or doing some sort of landmark

10   analysis where you look at how much blood pressure

11   they've lost in a certain period and then move

12   forward from there to look at strokes and to try

13   and adjust for those differences.

14        DR. WOERLE:  Yes, certainly we have in depth

15   looked into the relationship of drop in blood

16   pressure and potential occurrence of stroke.  And

17   our colleagues in drug safety have done numerous

18   analyses and could not find an association.  We

19   looked into outlier analysis in extremes.  Those

20   patients with the highest drop in blood pressure,

21   whether those were those patients who had a higher

22   risk of stroke, we didn't find any of these

1   associations.

2        I fully agree with you that, in general,

3   when you see a larger blood pressure drop, that you

4   should anticipate a benefit on stroke.  However,

5   what is important to keep in mind is the magnitude

6   of the blood-pressure lowering and also the

7   baseline blood pressure.

8        When you look into the recent ACCORD trial,

9   which is probably the best evidence we have, ACCORD

10   blood pressure, where a similar blood pressure

11   lowering was seen as in the EMPA-REG trial in the

12   diabetic population, I highlight on the diabetic

13   population.  Actually, no benefit on stroke could

14   have been observed.  And if any, one probably had

15   to wait much longer than the three years what we

16   have observed in this trial.

17        DR. SMITH:  Dr. Budnitz, you had a question.

18        DR. BUDNITZ:  Yes.  This is a question

19   regarding CV death in subgroup analysis, as

20   presented in the sponsor slide CO-54, but I use

21   that just as a starting point.  That shows the

22   overall hazard ratio of 0.62 in various subgroups

1    that are around 0.62.  But I think one subgroup

2    that isn't in the slide but in the very nice

3    materials, is by region.  And it seems like there's

4    much greater heterogeneity by region in not just

5    the cardiovascular death outcome, but I think all

6    outcomes, ranging from a hazard ratio 0.35 in Asia,

7    up to 0.81 that includes one in the confidence

8    interval in North America.

9         So I'm just wondering if I'm interpreting

10   this correctly.  I'm less concerned with the

11   confidence interval and more about the point

12   estimate being much closer to unity for North

13   America, and Europe as well.  It seems to be a

14   consistent finding across the outcomes.  And I'm

15   wondering if the sponsor has insights and make sure

16   I'm understanding this correctly.

17        DR. WOERLE:  Overall, our interpretation on

18   the cardiovascular death finding is that there's

19   actually very little heterogeneity with no

20   significant p-values for interactions.  We also

21   looked into the regional distribution and the

22   p-value for interaction was 0.14, not indicating

1    major interactions.

2         We looked into what from our point of view

3    is an at least as important analysis.  When you

4    look into white Caucasians, living most frequently

5    in North America and Europe, versus other

6    populations and the hazard ratio for the white

7    population is 0.64 with the upper bound being below

8    1, with a confidence interval of 0.83.

9         DR. BUDNITZ:  So just to clarify, you don't

10   think it's a significant difference between a

11   hazard ratio of 0.35 in Asia and 0.81 in North

12   America?

13        DR. WOERLE:  We have extremes.  We always

14   have certain extremes.  The test we apply is

15   significant interactions.  And when we look into

16   what drives the EMPA-REG OUTCOME results, the

17   majority of events come from North America and

18   Europe.  So the number of events being contributed

19   actually from Asia is less than 50.  And then when

20   you get into relatively lower numbers, you see

21   certain heterogeneity in the point estimate with

22   widening of confidence intervals.

1          DR. BUDNITZ:  Although there are equal

2     numbers from Asia and North America in the study?

3          DR. WOERLE:  What I'm saying is, when you

4     combine North America and Europe, it gives you the

5     most reliable estimate.  And when you combine North

6     America and Europe, the hazard ratio is virtually

7     identical to the 0.62.  And these are the two most

8     robust cohorts we have.

9          DR. SMITH:  All right.  Diana Hallare, you

10     had some questions much earlier today.  Again,

11     apologies for taking so long.

12          MS. HALLARE:  Hello.  This is also a

13     follow-up to Mr. Budnitz.  I would like to ask

14     about CO-54 and also CO-41, wherein the African-

15     American or black population, for instance, had a

16     higher hazard ratio.  And also if you would

17     consider the ages 30 to 59, especially the ages 45

18     to 59 population, they are more leaning towards the

19     placebo than towards the empagliflozin.

20          Also, I was wondering how could you explain

21     that effect?  I know there may be extremes in

22     certain populations, but do you think, for

1    instance, that the lipid effect could be a factor

2    in it or what could be possibly the background

3    processes behind the effects that are seemingly

4    extreme at this point?

5           DR. WOERLE:  Let's review briefly 3-point

6    MACE subgroup analysis, slide 2 up from the core

7    presentation.  It's correct that we saw some

8    heterogeneity when it comes to subgroups.  Subgroup

9    findings become particularly difficult to interpret

10   when you have about 50 or less events.

11          Now, we recruited in this trial 5 percent of

12   the overall population who identified themselves as

13   black or African-American.  These 350 patients

14   allowed us to make a reasonably robust assessment

15   on the overall safety of the compound, which did

16   not appear to be different from the overall

17   population.

18          We have also information from our phase 3

19   program where we also recruited African-American

20   and black population.  We did not identify any

21   differences in terms of blood pressure or response,

22   if any slightly more, but no major differences in

1    LDL or HDL cholesterol.

2         The most important and the striking finding

3    of the EMPA-REG OUTCOME trial is the CV death

4    finding.  And when you look into the CV death

5    finding -- slide 1 up please -- all hazard ratios

6    are on the left side of unity.

7         Now, a problem that I just mentioned is the

8    number of events and the widening of the confidence

9    intervals and the reliability of the point

10   estimate.  And one can see, for the African-

11   American population, the population seems to have a

12   similar effect as the overall population, but given

13   the lower number of events, there is greater

14   uncertainty.

15        But our overall conclusion is that in terms

16   of general safety, there is no difference between

17   the African-American population and the overall

18   population.  And in terms of CV death benefit, the

19   same statement holds true, with limitation based on

20   low numbers.

21        MS. HALLARE:  I would also like to ask about

22   the effects or interactions with other medications,

1    for instance with the beta blockers and the ACE

2    inhibitors, for instance.  So I was wondering if

3    that could have an effect on different side effects

4    or whether that could have had effect on the

5    lipids, for instance.

6          DR. WOERLE:  We looked into subgroups

7    prespecified as for ACE and beta blockers.  There

8    was no significant interaction with very similar

9    hazard ratios, 0.65 and 0.61 for ACE and the same

10    for beta blockers.  So there was no interaction.

11          MS. HALLARE:  Thank you.

12          DR. SMITH:  Dr. Neaton?

13          (No response.)

14          DR. SMITH:  Dr. De Lemos?

15          DR. DE LEMOS:  Yes, a question for FDA.  Can

16    you expand a little bit on the reluctance to

17    consider all-cause mortality in general as an

18    indication and specifically in this case where you

19    have a cardiovascular death finding that's out of

20    context already?

21          So how is that qualitatively different

22    than all-cause mortality, particularly given all

1     the challenges we've just talked about with regard

2     to classifying death?

3          DR. GUETTIER:  I'm going to call Dr. Temple

4     to the microphone.

5          (Laughter.)

6          DR. TEMPLE:  I'm not sure historically how

7     true that is, but you can think of a reason.  It's

8     hard to think of a drug that effects all causes of

9     mortality, so it doesn't make a whole lot of sense.

10     But we frequently look at all-cause mortality to

11     see if the beneficial effect on one subset is

12     countered by another.  So we are interested in it.

13          If you had a profound effect on

14     cardiovascular mortality and overall mortality went

15     the other way, you'd agonize a lot about what the

16     heck was going on.  But I think that's the reason.

17     It doesn't make sense that a drug would affect

18     specifically every single kind of mortality, and I

19     think that's why.  But I'm not sure we've -- we've

20     put it in labels.  We've shown the results.  So I

21     don't think there's a systematic conclusion.

22          DR. SMITH:  Dr. Cho?

1    DR. CHO:  Just a quick question about

2 regional variation in non-assessable cardiovascular

3 death.  Was there one particular region with higher

4 rates of inability to assess death?

5    DR. WOERLE:  I'm looking at my colleague

6 from drug development, Uli Broedl.  Can you answer

7 the question, please?

8    DR. BROEDL:  Uli Broedl, Medicine.  We

9 looked at presumed cardiovascular death, not only

10 in the overall population, but also per region, and

11 there was no difference in the occurrence of

12 presumed CV death per region, no difference.

13    DR. SMITH:  Dr. Schambelan?

14    DR. SCHAMBELAN:  So this refers to FDA's

15 slide 12 in the clinical assessment and to the

16 point about censoring the non-assessable deaths.

17 So, as a cardiovascular consultant pointed out, the

18 findings were still robust for CV death.  But if I

19 understand that slide correctly, there's no longer

20 superiority demonstrated for the 3-point MACE.  So

21 is that simply a matter of numbers, or what are we

22 to take from that difference?

1        DR. CHONG:  I just want to make sure I have

2  the question right.  So you want to know why on

3  slide 12 the statistical significance is lost for

4  3-point MACE when you exclude non-assessable death.

5  Correct?

6        DR. SCHAMBELAN:  The point was made earlier

7  that it's still a robust finding if those people

8  are excluded whom we don't know the cause of death.

9  The CV death is still a robust finding, but we lose

10  the superiority upper bound for 3-point MACE.  Is

11  that simply a matter of numbers?  I want to try to

12  understand that.  And that's my guess.

13        DR. SCHAMBELAN:  Right.  Fewer deaths that

14  feed into the 3-point MACE which is driving --

15        DR. WOERLE:  Lack of power.

16        DR. SMITH:  Okay.  That's resolved by the

17  data, by looking at these data again?  Or you're --

18        DR. GUETTIER:  You basically have less

19  endpoint events, and that's what you get when you

20  do the analysis whether or not -- of course it's a

21  retrospective analysis.  It also makes certain

22  assumptions, which may be valid or not valid, and

1    that's for everybody to decide.

2         DR. SMITH:  Dr. Rosenberg?

3         DR. ROSENBERG:  Thank you.  I'd like first

4    to push back a little against what Dr. Temple just

5    said, with all the respect I have for him.  The

6    patient who takes a new drug, he wants to know is

7    he going to live longer or not.  That's the bottom

8    line.

9         I understand from the drug development

10   clinical trialist point of view, it only makes

11   sense to look at overall mortality if you know the

12   drug has specific targeted effect if there's no

13   competing risk.  It looks like for this drug, this

14   class of drug, cardiovascular mortality is

15   overwhelming.  So I don't see any problem for using

16   overall mortality and getting rid of all this

17   adjudication and all this nonsense.

18        Now I have two questions, back to the data,

19   one about stroke.  I really don't understand how

20   and why the sponsor didn't look more carefully at

21   stroke in terms of separating hemorrhagic stroke

22   and ischemic stroke.  I haven't seen the data

1    clearly.

2            From the CEC point of view, sponsor, I don't

3    know why you included TIA, which has no clinical

4    meaning whatsoever when you compare it to the other

5    strokes.  It doesn't make sense to pool TIA with

6    stroke, so I'd like to see clearer on that.

7            The second question was regarding if we

8    started splitting and slicing data, let's continue.

9    And I'd be interested to see data by country,

10   country-specific data rather than region.  For

11   example, I don't remember having seen Western

12   Europe versus Eastern Europe, but where it was all

13   coded into different countries.

14           DR. WOERLE:  We've done these analyses.  We

15   have presented in the briefing book, but we're

16   happy to provide you the data.  And Dr. Sven

17   Koehler, who did extensive assessment will walk you

18   through.

19           DR. POCOCK:  So first of all, to clarify,

20   TIA was not included in the primary endpoint.  Only

21   strokes were included in the primary endpoint.

22   Second, if we looked into types of stroke,

1   hemorrhagic strokes were reported in less than 10

2   percent of the cases.  Slide 2 up, please.  So the

3   vast majority of strokes indeed were ischemic

4   strokes.

5         We went back retrospectively and further

6   evaluated the types of stroke and asked the

7   adjudication committee to assess the respective

8   types of strokes.  And I would like to ask

9   Dr. Bernstein to comment on that.

10         DR. BERNSTEIN:  Can we have slide 2 up,

11   please?  Richard Bernstein, stroke neurology from

12   Northwestern.  If you look at the vast majority of

13   strokes in this study, they were ischemic.  And as

14   the panel knows, ischemic stroke is really not just

15   one disease.  It's several diseases.

16         So, for example, large artery

17   atherosclerosis is a quite different disease than

18   small vessel occlusion, which are both quite

19   different than cardioembolic stroke, which is due

20   usually to atrial fibrillation.  And undetermined

21   etiology, which accounts for a sizeable number of

22   strokes here, is a grab bag of different biological

1 processes.

2   What you can see here is the relative number

3 of events in the placebo and empagliflozin arms,

4 and there's a non-specific increase in all types of

5 events, which to me is not a biologically plausible

6 result since all of them are different mechanisms.

7   DR. SMITH:  Is that a follow-up related to

8 this, Dr. Good, related to this same point?

9   DR. GOOD:  Yes, just a follow-up of that.  I

10 read in one of the reports that the drug group had

11 a lower use of anti-platelet agents and

12 anticoagulants and had a higher risk of atrial

13 fibrillation.  And I wondered if that might

14 possibly explain some of the apparent difference,

15 maybe not the whole thing.

16   DR. WOERLE:  It's correct, we saw some

17 subtle differences in the use of anticoagulative

18 medication.  We saw some differences in the

19 regional distribution.  You saw the data this

20 morning in Europe that the stroke rate was much

21 lower in the placebo group, being suggestive that

22 they might have received more comprehensive

1    preventive medication.  But when we looked into the

2    data, we could not establish a clear association.

3          DR. SMITH:  Dr. Palevsky, you had a

4    question?

5          DR. PALEVSKY:  So we haven't talked much

6    about the kidney disease aspect.  And looking at

7    your presentation versus the agency's presentation

8    and your briefing materials, in your combined

9    outcome of new or worsening nephropathy, I'm

10   confused by the renal replacement therapy, which is

11   described in some places as continuous renal

12   replacement therapy and in others as renal

13   replacement therapy.

14         As the agency points out, continuous renal

15   replacement therapy is a treatment that is almost

16   exclusively used in patients with acute kidney

17   injury in the setting of critical illness.  So can

18   you clarify that aspect of the endpoint and what

19   you were really assessing there?

20         Then the other is the doubling of serum

21   creatinine and eGFR of less than 45, which again

22   can represent either acute disease or chronic

1    disease.  So can you provide additional granularity

2    on how you know or don't know that this is

3    progression of chronic disease for these patients?

4         DR. WOERLE:  Certainly.  Can I have slide 2

5    up?  And may I ask Dr. Kim to join me?  And one of

6    the limitations of the data we have on the EMPA-REG

7    OUTCOME trial that indeed events were not

8    adjudicated, which leaves us with a certain degree

9    of uncertainty when it comes to the initiation of

10   renal replacement therapy.  What is the striking

11   finding that all components of the composite are

12   going in the same direction, but we are aware of

13   the limitation given small numbers.

14        But you specifically asked on acute versus

15   chronic kidney renal replacement therapy, and Dr.

16   Kim will provide you the answer.

17        DR. KIM:  So to clarify the first question,

18   which was pertaining to is this actually chronic

19   renal replacement therapy or acute renal

20   replacement therapy, it was a mixture of both.

21   Slide 3 up, please.  So, when we did the analysis,

22   both acute initiation of renal replacement therapy

1   and chronic renal replacement therapy were

2   included.  And the endpoint that would show us in

3   terms of initial renal replacement was a

4   combination of both.

5        When we look at specifically chronic renal

6   replacement therapy, indicating a start and

7   continuation of replacement therapy until the end

8   of the trial, we saw fewer numbers, but the hazard

9   ratio was still similar to what we observed for the

10  total.  The second question was pertaining to GFR

11  doubling of creatinine.

12       DR. PALEVSKY:  So verification that the

13  doubling of serum creatinine and eGFR was a

14  persistent decline of that rather than representing

15  either biological variation or true acute kidney

16  injury.

17       DR. KIM:  The doubling of creatinine was

18  also a singular measurement of doubling of

19  creatinine, and that would have made that endpoint.

20  Slide 2 up, please.  So the first row indicates the

21  number we have presented, the doubling of serum

22  creatinine, and lower than 45 mLs per min per 1.73

1    meters square.

2         When we look at sustained doubling of

3    creatinine, which would be defined as a measurement

4    after 30 days having a continuous doubling of

5    creatinine, the numbers do decrease.

6         When we look at other modern endpoints, such

7    as sustained 50 percent decrease in eGFR or

8    sustained 40 percent of decrease in the eGFR, the

9    numbers again increase.  But looking at the hazard

10    ratios, they continued to be consistent with the

11    initial finding based on single creatinine

12    measurements.

13         DR. SMITH:  Dr. McBryde?

14         DR. MCBRYDE:  I'm going to follow up on

15    Paul's inquiry about the kidney.  I had a question

16    for both the sponsor and for FDA.  For the sponsor,

17    a couple of quick questions.  One, I was curious

18    which MDRD formula that you used.  I presume it was

19    probably demographics and serum variables because

20    I'm curious if there were urinary assessments done

21    as part of the evaluation.

22         DR. WOERLE:  Dr. Broedl will provide you the

1    answer.

2         DR. MCBRYDE:  Thanks.

3         DR. BROEDL:  Uli Broedl, Medicine.  You are

4    correct, there were no urinary samples or data that

5    were included.

6         DR. MCBRYDE:  Then I couldn't find in the

7    materials the urine albumin to creatinine ratios.

8    How were those standardized, and do you know what

9    assay was used for the measurement of the albumin?

10   Was it a turbidimetric, a nephelometric,

11   radioimmunoassay?

12        DR. BROEDL:  So I can't answer this on top

13   of my head.  All I can say right now is this was

14   based on spot urine measurement and at regularly

15   defined visits where we took safety levels.

16        DR. MCBRYDE:  In that spot, do you know if

17   they were first morning urines, or if they were

18   random samples?

19        DR. BROEDL:  Our trial protocol, the visit

20   usually should have been in the morning, so the

21   presumption is first morning visits, but this was

22   not fully standardized.

1          DR. MCBRYDE:  Thank you.  And then for FDA,

2    I wanted to follow up on slide 23.  You had

3    analyzed the data after the wash-out looking at the

4    albuminuria.  I was curious if you had done a

5    similar analysis looking at the eGFR measurements

6    and the blood pressure measurements.

7          DR. LUNGU:  The eGFR does go up.  I don't

8    recall for blood pressure, but I think it does as

9    well.  But the eGFR we did not present, but it does

10   go up.

11         DR. MCBRYDE:  Thank you.

12         DR. GUETTIER:  I think the sponsor had the

13   eGFR figure in their talk.

14         DR. WOERLE:  Yes, slide 1 up, please.  So

15   does this speak for itself, or do you have

16   questions?

17         DR. MCBRYDE:  Thank you.

18         DR. WOERLE:  We did similar measurements for

19   blood pressure and blood pressure values came back

20   to baseline.  And the difference at the end of the

21   trial is approximately 4.5 milliliter.

22         DR. MCBRYDE:  Thank you.

1          DR. SMITH:  So where we are -- yes,

2     Dr. Palevsky?

3          DR. PALEVSKY:  On that last slide, just

4     since you have switched from using MDRD at another

5     point and using CKD-EPI here, which CKD-EPI

6     equation?  Is this creatinine?  Is this creatinine

7     cystatin-C?  So which equation are you looking at,

8     and why are you switching eGFR calculation methods?

9          DR. WOERLE:  Okay.  We have Dr. Wanner with

10    us.  He's the first author on the recently

11    published New England Journal who is best equipped

12    to provide you this answer.

13         DR. WANNER:  Christoph Wanner, University of

14    Würzburg.  I appreciate to respond to your

15    question.  I think the first one you were asking

16    was CRRT, continuous rental replacement therapy.

17    It was a language issue.  When I came in, I

18    corrected this.  This is dialysis.  It's not CRRT

19    on the intensive care unit.

20         The albumin measurement was nephelometric.

21    The four laboratories forming the core laboratory

22    were using the same assay.  The creatinine was

1    enzymatic measurement and it was isotope dilution,

2    mass spectrometry corrected, so standardized.  And

3    the MDRD formula was introduced in 2010, and we

4    decided to do so because at this time, the CKD-EPI

5    was not validated across the globe and the MDRD for

6    an entry criteria.

7         But then the reviewer from the New England

8    Journal paper asked us subsequently, you can use

9    the CKD-EPI to create the slopes since the

10   creatinine is standardized.  And then we switched

11   to creatinine.  And cystatin-C, we only measured in

12   a thousand patients and this is not in this

13   analysis.

14        DR. SMITH:  So given where we are on the

15   clock, I would like to move to the discussion

16   questions.  There were a few people who had their

17   hands up for clarifying questions.  So I want to

18   move forward, but if there are questions remaining

19   that you feel are important before we move related

20   to the discussion questions, we'll entertain those.

21   So is that -- yes, Dr. Konstam?

22        DR. KONSTAM:  I don't know if this really

1    even needs an answer, but with regard to what

2    occurred at the time of the interim analysis, the

3    sponsor said something to the effect of a Chinese

4    wall or complete protection between the people who

5    were unblinded and not.  The FDA presentation said

6    there were 230 individuals unblinded.

7         It's kind of inconceivable to me that 230

8    people can keep their mouths shut for two years or

9    whatever it took.  I mean, that could be a comment.

10   If the sponsor wants to answer it, I guess that

11   would be okay.

12        DR. WOERLE:  We have implemented, after the

13   agreement with FDA on the conduct of the trial and

14   the interim analysis, a comprehensive plan to

15   maintain trial integrity.  All individuals had to

16   sign confidentiality agreements.

17        DR. KONSTAM:  No, I'm sure you did the best

18   you can.

19        DR. WOERLE:  We undertook every effort, but

20   at the end of the day, you're right.  Effort is

21   nice, but what is the outcome of your effort?  And

22   what gives us the greatest reassurance, when you

1    look into the primary endpoint and the components

2    of the primary endpoint and when you look at

3    patients being included prior to the interim

4    analysis and those patients being included after

5    the interim analysis, that you basically get almost

6    virtually identical hazard ratios.

7            **Questions to the Committee and Discussion**

8            DR. SMITH:  Okay.  We will now proceed with

9    the questions to the committee and the panel

10    discussions.  And I just want to remind public

11    observers that while the meeting is open for public

12    observation, public attendees may not participate

13    except at the specific request of the panel.

14            We'll go to the first discussion question,

15    and I will read this.  Discuss your interpretation

16    of the EMPA-REG OUTCOME study conduct.  Please

17    comment on whether interim unblinding, or changes

18    made to the protocol, endpoint definitions, and

19    analysis plan, for example specific exclusion of

20    silent MI from the primary endpoint, during the

21    course of the EMPA-REG OUTCOME study alter or do

22    not alter your level of confidence in a conclusion

that excess CV risk was excluded, and CV benefit

was established.

So I'll open that for discussion or for

comment from members of the panel.  Dr. Hiatt?

DR. HIATT:  Thanks.  Well, these points have

already been made.  And this trial was primarily

designed as a trial to exclude a certain level of

cardiovascular risk, and it was repowered to be

able to establish superiority.  When you sort of

play with those numbers, the event rate on placebo

was 4.4 percent, which is kind of a standard event

rate.  It's not super high.

If you're trying to power for efficacy in a

cardiovascular outcome trial with say a hazard

ratio of 0.85, you need about 1200 or 1300 primary

events.  So 600 events seems kind of low to me for

a primary MACE endpoint, which left me a little bit

confused as to really what the intent of the trial

was.  I think it's easiest to interpret the trial

on establishing non-inferiority, and it's a little

more challenging with the MACE primary to establish

superiority.

1          I think the other components of these

2     questions, including silent MI, may be easier to

3     answer in number 2.

4          DR. SMITH:  Yes, Dr. Konstam?

5          DR. KONSTAM:  Well, the question basically

6     is, are we influenced by these things we've been

7     concerned about in the trial.  And I guess I am

8     really principally because so much rests on the

9     p-value for the superiority for the MACE 1 endpoint

10    that sits at about 0.04.

11         There are issues about maintaining the blind

12    during the interim analysis.  There are issues of

13    missing data for the MACE 1 endpoint, MACE 3

14    endpoint.  There are issues about silent MI, which

15    I'm not so concerned about as an individual thing.

16         But I guess, in aggregate, I guess I am

17    concerned about them really because, you know for

18    that endpoint of MACE 3, which I believe is really

19    important here, it's a marginal figure to begin

20    with.

21         DR. SMITH:  So again, to follow up that, I

22    think in the discussion question itself, at least

1    as the FDA wrote it, they've really focused -- they

2    don't mention MACE 3 and they're really focusing on

3    cardiovascular risk.

4            I back off.  I've reread the question.

5    Cancel my last two sentences.  Other comments on

6    this?  Dr. De Lemos?

7            DR. DE LEMOS:  I just think with the

8    indication, it's not relevant.  Right?  I mean,

9    we're talking about a cardiovascular death

10   indication and these are all important issues.  The

11   silent MI is an important issue, but we're talking

12   about cardiovascular death, not the primary MACE

13   component.  So frankly, the blinding issues are

14   less important there, too.  And whether there was a

15   firewall leak, when we're talking about a death

16   endpoint, I think these issues kind of wash out.

17           DR. SMITH:  Other comments?  Dr. Neaton?

18           DR. NEATON:  I mean, I've been involved in a

19   number of trials where we've measured silent MI.  I

20   would agree with what the sponsor and I think the

21   FDA is concurring, that they just dropped that.  I

22   think that's a bit of a mess, and so I think they

1    just went about doing it incorrectly, and possibly

2    labeled it incorrectly.

3        When I measure silent MI, you want to make

4    certain the surveillance of people in the 2 groups

5    is done comparably over the whole course of

6    follow-up, which typically means ECGs at standard

7    intervals, and comparing serial ECG change.  And so

8    they didn't do that from the start.

9        I share Dr. Konstam's concern about the

10   MAC 3.  I have to say though, I was reassured with

11   two things in the FDA analyses.  One, they did

12   address, at least to a limited extent, the impact

13   of missing data.  And they're right on the border.

14   The upper bound of that confidence interval was

15   0.996.

16       The other thing they did, which relates to

17   some of the earlier discussion, which I think was

18   actually reasonable potentially in a trial where

19   you expect a large fraction of the deaths to be

20   cardiovascular, is simply change your composite to

21   look at fatal/non-fatal MI, and stroke, and all-

22   cause mortality.  And in that situation, the result

1  is actually stronger.

2      I think while trials can always be done

3  better in terms of follow-up, the sufficient

4  analyses led me to kind of have some reassurance

5  and confidence in at least the outcome that we're

6  going to be talking about later.

7      DR. SMITH:  Dr. Cooke?

8      DR. COOKE:  I think the aspect of the study

9  design or conduct that bothers me the most was that

10  large percentage of deaths that were unassigned or

11  uninterpreted.  I forget what the exact term is.

12  But the fact that 40 percent of the deaths were not

13  defined and had to be put into the presumed

14  cardiovascular death, the fact that's such a large

15  percentage, does bother me.

16      I think the FDA made the point that what you

17  do with those -- it's important what you do with

18  them, but those numbers should be relatively small.

19  And especially if we're trying to discuss an

20  efficacy trial where 40 percent of the deaths we

21  don't know what the cause is, that bothers me.

22      Now, that's mitigated a lot by a number of

1    the other sort of analyses.  The fact that

2    all-cause mortality was significantly lower with

3    the treatment, and the fact that the sensitivity

4    analyses in a number of ways, whether you assign

5    them to all cardiovascular or not cardiovascular,

6    or eliminate them completely, the data are

7    supportive of efficacy.  But again, I think that

8    number does stick out a lot to me.

9              DR. SMITH:  Dr. Rosenberg?

10             DR. ROSENBERG:  Yes, I agree with Dr. Neaton

11   and Dr. Cooke's comments.  I mean, that bothers me

12   not because it seems to change the outcome, but it

13   bothers me about what else has happened during the

14   study conduct that we don't know.

15             The fact that such a large trial with so

16   much monitoring, they see such a level of

17   uncertainty about so many things related to the

18   outcomes, and I assume other things that we're not

19   sure how the data was collected so that we're not

20   able to validate those critical elements, that does

21   bother me.

22             DR. SMITH:  Dr. Proschan?

1          DR. PROSCHAN:  I was initially troubled by

2     the fact that it seemed like perhaps people were

3     seeing results and that's what caused them to

4     resize the trial to show benefit.  But after

5     hearing the FDA's presentation, I'm convinced that

6     that's not what happened because the FDA actually

7     encouraged them to increase the size of the trial

8     rather than have a separate trial.  So that doesn't

9     bother me anymore.

10         Also, the undetermined cause of death

11    doesn't bother me that much because the all-cause

12    mortality result was significant.  And I disagree a

13    little bit with Dr. Temple.  I usually don't

14    disagree with Dr. Temple.  I know better.

15         (Laughter.)

16         DR. PROSCHAN:  But I think when you say that

17    there's a benefit on all-cause mortality, you're

18    not saying, this benefits every single cause of

19    mortality, you're just saying there's a benefit on

20    mortality.  Most of the mortality is

21    cardiovascular, and so I think it is meaningful if

22    you prefer to not say all-cause, just say there's a

1    benefit on mortality.  I think that's substantiated

2    from the results here.

3         DR. SMITH:  Thank you.  And Dr. Everett?

4         DR. EVERETT:  Just a quick comment that I

5    think the fact that the primary, the endpoint that

6    we're discussing here is a mortality endpoint.  As

7    Dr. De Lemos said earlier, it makes this much

8    easier in some respects because, as the sponsor has

9    pointed out, it's not like we're misclassifying

10   somebody as alive versus dead.

11        We're convinced they're dead.  It's just a

12   question of classifying them as cardiovascular

13   versus non-cardiovascular.  And depending upon how

14   you draw that line, the benefits are present in

15   both groups or more substantially in cardiovascular

16   death.

17        I think the wandering road that the trial

18   took organizationally is notable.  And I bet if the

19   sponsor could have a do over, they probably

20   wouldn't have as many amendments and readjustments

21   and realignments.  That said, I'm not convinced

22   that those had a material effect on the outcome or

1    in my confidence of the outcome.  If we were

2    talking about a different endpoint than mortality,

3    my answer there might be substantially different.

4          DR. SMITH:  Dr. Cho?

5          DR. CHO:  Thank you.  I think for me, the

6    most interesting part was reading the recently

7    published LEADER trial, which also had a placebo

8    cardiovascular death rate of 6.0 percent, which is

9    very similar to the death rate in the EMPA-REG

10   OUTCOME study, which actually reassured me a great

11   deal.  Even though there was a 40 percent presumed

12   non-assessable cardiovascular death, it's

13   remarkably similar to another diabetic trial.

14          DR. SMITH:  Dr. Fradkin, did you have a

15   comment?

16          DR. FRADKIN:  So I just looked up the

17   methods, the design paper for the study, which was

18   submitted in May of 2014.  And even then, they were

19   describing as a significant secondary outcome the

20   time to individual occurrence of silent myocardial

21   infarction.  So I am confused by this sort of

22   wandering course.

1           I'm just wondering why, if shortly before

2      the study ended, they said that this was in fact a

3      significant secondary outcome and they were doing

4      these EKGs, I don't understand how in this kind of

5      timeframe it sort of -- we lost silent MI.  And I

6      am concerned because it looked, from the data, like

7      silent MI might have been a hazard signal.

8           I feel like even though what they're asking

9      for is cardiovascular mortality, from the

10     statistical perspective, you wouldn't be able to

11     consider that sort of part of a composite outcome

12     if you didn't think that the composite outcome was

13     solid.  So I think I get back to what Dr. Konstam

14     said.  The 0.04 is not super strong.

15          Now, that was not including -- they never

16     included silent MI, as far as I can tell, in this

17     design paper in the composite, but I think sort of

18     the whole variability of it does lead you to

19     question whether the composite outcome was strong

20     enough to get back to what was said in the initial

21     FDA presentation about not needing two trials.

22          DR. SMITH:  Yes, Dr. Konstam?

1          DR. KONSTAM:  I just maybe want to engage my

2     colleagues a little bit because I'm hearing people

3     viewing what's going on here in different ways.

4     And one of the comments around the table has been

5     well, you know, the real meat is going to be in the

6     cardiovascular death endpoint, so the MACE 3

7     endpoint may not be as important.  And I'm kind of

8     not thinking exactly along those lines.

9          Let me just ask folks this.  If the p-value

10    for the MACE 3 endpoint were 0.07 instead of 0.04,

11    and the CV death and all-cause death were exactly

12    the same as they are, would we be saying the same

13    thing?

14          I think the answer is no because I think you

15    won't have hit the endpoint that gets you to look

16    at the cardiovascular death, and you've lost the

17    hierarchy even one level up.  So I think, at least

18    the way I'm thinking about it, whether or not the

19    MACE 3 endpoint is positive or not to me is real

20    important in terms of whether we should even be

21    considering the cardiovascular death endpoint.  But

22    I don't know if -- I'm willing to be dissuaded from

1    that if people think --

2         DR. SMITH:  Dr. Thomas?

3         DR. THOMAS:  I actually agree with you

4    completely.  If the MACE 3 endpoint did not meet

5    significance, we probably wouldn't be having this

6    meeting.  You would have an intriguing finding that

7    there's less cardiovascular deaths and less deaths

8    overall, and you'd probably require another trial

9    to prove the point.

10        So there's a little bit of luck that these

11   cases that were deemed to be cardiac were put into

12   that category.  If they were excluded as

13   non-cardiac deaths, as the FDA data shows, your

14   point estimates become larger, you're not

15   significant, and that's probably just due to having

16   less events to decide this.

17        So in a way, the sponsor is lucky that it

18   fell in a significant way.  And I think that's the

19   ultimate decision, do you feel that that's enough

20   to sway with all the other evidence.  It did meet

21   the primary endpoint, but there are some issues

22   with the data and the data collection, and how much

1    of that is going to play the role.

2            The only thing is no one's addressed the

3    other part of this question, which is, has CV risk

4    been excluded.  And I think, actually, that seems

5    to be fairly confident that that has been excluded.

6    But I agree, I think the 3 endpoint has to be the

7    crux of whether you make this decision or not.  If

8    you're comfortable with that being significant,

9    then you can go along the rest of the pathway.

10           DR. DE LEMOS:  Why?  I mean, why would we

11   interpret it that way with the p-value?  I mean,

12   it's a probabilistic statement.  The finding is

13   completely out of context, the mortality finding,

14   and we're evaluating an out-of-context standalone

15   mortality finding with an incredible p-value and

16   trying to decide.  They're not asking for an

17   indication for reduction in the MACE endpoint.

18   They're asking for an indication of cardiovascular

19   death.

20           I guess it fails the common sense test to me

21   to say that we will consider this.  Would we rather

22   be considering an indication where the primary

1    endpoint hit at P equals 0.48 and the

2    cardiovascular death and total mortality were

3    borderline non-significant?  We give them that

4    indication, but we won't give them a mortality

5    finding?

6         This is a much stronger result for patients

7    and for the drug.  Whether it's enough to stand

8    alone as a single trial is a separate point.  I

9    mean, that's a different question.  But it makes

10   zero sense to me to take this -- this finding is

11   clearly out of context with the composite.  There's

12   no explanation within the composite for why one

13   sees this degree of mortality benefit.  It's

14   unexplained and it stands alone, not as a component

15   of the composite.

16        DR. SMITH:  Yes, Dr. Konstam?

17        DR. KONSTAM:  Well, it's the last question

18   where we'll start drawing conclusions, right.  So

19   I'm listening to my colleagues as you are.  But

20   there are a number, I'm sure, as you know, of prior

21   cardiovascular trials where there was a

22   statistically significant benefit on either

mortality or cardiovascular mortality that was not

the primary endpoint and was not in the hierarchy

of secondary endpoints.

It might have been a down-the-road secondary

or an exploratory endpoint. It might have been

something that was looked at post hoc. It might

have been something that came out of a subset

analysis. And now, in all of those circumstances,

well, at least the ones I'm thinking of, when it

was replicated in a trial specifically designed to

look at mortality, it didn't show up at all.

Now, there are things maybe that can get us

there. Okay? But I mean, I would stick to the

point that we approach questions in a clinical

trial in a hierarchal format in order to retain

alpha. And for this particular endpoint of

cardiovascular mortality, we're out of alpha. So

why would you -- let's say if it were something

else, I mean, I think we're affected by the fact

that it's mortality, but we still want to get it

right.

Let me just make one more point. I think

1    there are things that could influence us despite

2    that to say, yes, but I'm going to go with it

3    anyway, for example, a very, very, very low

4    p-value.  The problem I have with that -- and I

5    respect Dr. Pocock, but I don't think that the real

6    p-value is calculable in a setting like this where

7    we just have an endpoint that's floating, where we

8    really don't have it in the hierarchy, but maybe

9    that could influence this.

10          The second thing that might influence us is

11   the number of events.  Okay?  So there are 300

12   some-odd events, cardiovascular mortality events.

13   And we might say it really is about the number of

14   events, that's a critical factor.  Those could help

15   us get there I guess, but I really would

16   stick -- if you want to be rigorous about it, you

17   believe something if you got to it in a rigorous

18   statistical way.

19          DR. SMITH:  Dr. Thomas, respond.

20          DR. THOMAS:  I think to just add to what you

21   mentioned is really the crux of this in terms of

22   the final decisions that are made, is this

1    sufficient based on what we have to be a single

2    trial to give this indication.  I was on the

3    committee for the JUPITER trial, which was a much

4    larger trial and I think it was much clearer.  And

5    even then, there was some hesitation about a single

6    trial, no matter how well done, to get an

7    indication like this.

8            So really, that's going to be the end

9    question that people ask, is this one trial, based

10   on these factors, even though the cardiovascular

11   reduction and mortality is, from what the data is,

12   is dramatic, going to be enough to require another

13   trial or is this sufficient.

14           DR. SMITH:  Dr. Wilson?

15           DR. WILSON:  So to build on what was just

16   said, I think what we're missing is a plausible

17   really well-defined and substantiated mechanism.

18   So we have glucose, and it doesn't appear to be

19   glucose.  We have blood pressure.  The blood

20   pressure effects are not real big.  We have heart

21   failure.

22           Throughout this meeting, the heart failure

1 information has really been downplayed because it's

2 not like what we've seen for some of the other

3 studies for heart failure.  And some of the

4 definitions of heart failure admissions are rather

5 short-term admissions.  And also some of it's

6 change in medication programs.

7    I think that's why we're circling back to

8 what Marv Konstam's been saying, how did we get

9 there?  And can we really say this is it for a

10 death outcome, but we're not sure how we got there?

11 So I still have some concern about how we got there

12 and raise the hierarchal issues that were

13 originally raised almost as the very first question

14 of the day by Will Hiatt.  Important issue.

15    DR. SMITH:  Who had his hand up again, Dr.

16 Hiatt?

17    DR. HIATT:  I feel we're wandering between

18 question 1 and question 2.  And so in terms of

19 strength of the evidence and trying to dissect what

20 this means, I think I'll hold off until question 2.

21    DR. SMITH:  Dr. Palevsky?

22    (No response.)

1    DR. SMITH:  Dr. Rosenberg?

2    DR. ROSENBERG:  Yes, maybe I should hold

3    off, but I'll go anyway.  Well, in fact, it's two

4    questions.  One, related to what's just been said,

5    I really agree that we didn't get a clear

6    explanation of the mechanism.  And especially when

7    you see at the divergence of the curve within the

8    first three months, which is almost unheard of, I

9    heard talking about hemodynamic but really without

10   clear explanation about what that means that

11   explains such a drop in mortality.  Patients in

12   this study didn't seem to have severe heart

13   failure, or any other problem that would explain

14   that.  So I'm really puzzled by that.

15       My second question, again, may happen later

16   with answering the question is to the FDA.

17   DR. SMITH:  I'm hesitant to ask more

18   questions because, really, at this point, if it's

19   something that will critically affect this

20   discussion, okay.

21   DR. ROSENBERG:  Yes.

22   DR. SMITH:  But we've sort of moved beyond

1    questions to us discussing what we got.

2         DR. ROSENBERG:  I think it will, at least in

3    my mind.

4         DR. SMITH:  All right.

5         DR. ROSENBERG:  Is there any precedent for

6    this kind of study or other of the FDA having given

7    regulatory approval based on the component, the

8    positive outcome on one component of a composite

9    endpoint when the composite endpoint was the one

10   that was approved by the FDA as the primary

11   outcome?

12        DR. SMITH:  Does FDA have a quick answer to

13   that?

14        DR. STOCKBRIDGE:  I would say we routinely

15   dissect out a component and try to figure out

16   whether or not all of the components actually

17   contribute to it.  And I don't even think, when we

18   do it, we insist that any one of the components

19   actually ends up being statistically significant in

20   order to name it.  It's mostly about trying to weed

21   out components that clearly don't contribute to the

22   overall observed effect.  It's done for descriptive

1   purposes.

2         DR. TEMPLE:  I can give you an example.

3   What Norm said is right.  When you have a composite

4   that's made up of multiple different things, why

5   would you even expect they all go the same way?

6   But the LIFE study comparing atenolol and losartan

7   had a composite endpoint the same as this, and it

8   won nicely showing that losartan was better.

9         When we look closely, all of the benefit was

10   on stroke.  There was no hint of a benefit on MI or

11   anything like that, but fatal and non-fatal stroke

12   was responsible for the whole thing, and that's

13   what the label says.  That's the claim they got.

14   We also noted that it didn't work in the black

15   population.

16         So you do look at these things, and how to

17   do it, and whether that makes sense, and whether

18   you've corrected for multiplicity is a very good

19   question.  But as Norm says, you sort of have to

20   look.

21         DR. KONSTAM:  Can I just follow through with

22   a question to you, Bob?  But what trial were we

1      just talking about?

2            DR. TEMPLE:  LIFE.

3            DR. KONSTAM:  LIFE.  But the primary

4      endpoint of the LIFE trial was positive.  Right?  I

5      don't remember the p-value.  I think it was a

6      pretty low p-value.

7            DR. TEMPLE:  You're exactly right.  You had

8      to win on the primary endpoint --

9            DR. KONSTAM:  Right.

10           DR. TEMPLE:  -- which is what you said.

11           DR. KONSTAM:  So you could have chosen how

12     to word the indication, but what would you have

13     done with that stroke finding if the primary

14     endpoint did not hit statistical significance?

15           DR. TEMPLE:  No, no.  What you said before

16     was right.  It's presumed that you have to win on

17     the primary endpoint.

18           DR. KONSTAM:  That's right.

19           DR. TEMPLE:  That's right.  And that's one

20     of the -- that's why you're asking that here.

21           DR. KONSTAM:  Just to dissect that one step

22     further, you also like to see two trials.  So you'd

1  like to see -- if you're going to go with one

2  trial, you'd like to see a pretty low p-value in

3  that primary endpoint.

4       DR. TEMPLE:  Well, in LIFE, we didn't have a

5  very low p-value.

6       DR. KONSTAM:  It wasn't that low?

7       DR. TEMPLE:  No.

8       DR. KONSTAM:  What was it?

9       DR. TEMPLE:  I mean, it wasn't 0.001 or

10  anything.

11       DR. KONSTAM:  I'm going to look it up.  I'm

12  going to look it up.

13       (Laughter.)

14       DR. TEMPLE:  It was better than 0.04.

15       DR. HICKS:  I really need to speak up about

16  this because I believe that the heart failure

17  findings in this trial are not reliable.  I looked

18  at a bunch of the CEC packets on heart failure and

19  a lot of the events that were adjudicated as heart

20  failure hospitalizations shouldn't have been

21  adjudicated as such.

22       Also, what I found in my review is that

1   events were being adjudicated as heart failure, and

2   they did not even meet the criteria of the CEC

3   definition.  And based on my review, I found that

4   probably the definition that was used by the CEC

5   got further diluted to mean any ER visit and any

6   oral dose of Lasix.

7        Lastly -- and perhaps Dr. Januzzi can

8   provide some additional information on this -- it

9   appeared that these events were being

10  double-counted.  So if patients came in with a

11  myocardial infarction and they had heart failure

12  secondary to the myocardial infarction, these

13  events were being double-counted as a myocardial

14  infarction and also as a heart failure

15  hospitalization.

16       So I think if the applicant can speak more

17  about this -- but this is what was found in the

18  adverse events datasets and also in the time-to-

19  event CEC datasets.

20       DR. SMITH:  So does the applicant have a

21  response to that, just briefly?

22       DR. JANUZZI:  Thanks for the opportunity to

1   respond.  It is true that there were cases of

2   patients that would present with heart failure and

3   at the same hospitalization, they would have

4   myocardial infarction adjudicated as well.  One

5   important thing to emphasize is that we adjudicated

6   the myocardial infarctions within the context of

7   the universal definition of myocardial infarction

8   wherein type 2 or so called supply/demand infarct

9   is not an uncommon scenario in the context of heart

10  failure hospitalization.  So that's just one

11  situation I'd emphasize.

12        Relative to other specific individual

13  concerns, I would say when we adjudicated cases, we

14  adhered to the CEC charter for the definitions.  I

15  can't speak to individual examples, but that's

16  obviously something you've had the opportunity to

17  look at.

18        DR. HICKS:  So yes, I did see those cases

19  with type 2, but there were cases of type 1 MIs and

20  heart failure was associated with the type 1 MIs,

21  and there was double-counting of events.

22        DR. WOERLE:  We conducted various

1    sensitivity on heart failure outcome.  Slide 3 up.

2    We used the adjudicated events as being described

3    in the main presentation.  We used loop diuretic

4    introduction as a proxy for hospitalization, for

5    new hospitalization.  And we used the introduction

6    of loop or heart failure.

7         You see, we did the same analysis on

8    e-reporting on heart failure and we get always very

9    consistent findings.  Slide 2 up.  This is based on

10   symptoms, so edema, serious adverse events and

11   heart failure reporting.  Slide down, please.

12        DR. SMITH:  Dr. Proschan, did you have a

13   comment?

14        DR. PROSCHAN:  Yes.  I think we are

15   encroaching on question 2, and that one actually is

16   encroaching on question 4.  But I just wanted to

17   comment on, y if the p-value for MACE 3 had been

18   0.07, would we even be here.  I think we definitely

19   would be here.

20        This secondary outcome is not feelings of

21   dread and foreboding.  It's cardiovascular

22   mortality and it's overall mortality.  I think we

1 would definitely be here.  And I think we do need

2 to consider it.

3 I know that there are people who say, okay,

4 if you don't get a significant result on the

5 primary, you can't look at anything else.  But if

6 you're looking at mortality and you're seeing a

7 highly significant p-value, even after you make a

8 pretty strong adjustment for mortality -- I mean

9 for multiplicity, sorry -- I think that is pretty

10 compelling.

11 On the other hand, the one thing I will say

12 is there's always more multiplicity than you think

13 because you could consider well all the different

14 ways to analyze the data, the different components

15 of each outcome, when you add all that up, I think

16 it's more than 42.  I'd be willing to bet a lot of

17 money that it's more than 42.

18 DR. SMITH:  Dr. Cho, did you have a comment?

19 DR. CHO:  I wanted to say that the MACE that

20 we're looking at in EMPA-REG is an athero MACE,

21 atherosclerotic event MACE.  And the mechanism of

22 this drug is probably not its benefit on

1    atherosclerosis, and I think that we should all be

2    sort of mindful of that.

3            Traditionally, we've always accepted MACE as

4    sort of the athero MACE, the MI, stroke, and

5    whatnot, but I think we come to an area now where

6    we have some -- who knows what mechanism to

7    decrease cardiovascular mortality through a

8    different mechanism.  So that's my one comment.

9            My second comment is, recently there's been

10   a paradigm heart failure study looking at ENTRESTO

11   and their primary outcome was death and CHF

12   hospitalization, which is an accepted endpoint for

13   heart failure trials.  They redid the analysis

14   looking at a softer heart failure endpoint, as was

15   done in EMPA-REG, visits to the ER, increase in IV

16   diuretics.  And not surprisingly, the death rate

17   with these soft endpoints was also reduced with

18   ENTRESTO.

19           So I think that in the light of 30-day

20   readmission and people trying to get patients not

21   admitted to hospitals, looking at these sort of

22   24-hour emergency room visits is not out of

1    ordinary.  And we will be seeing this more and more

2    throughout other trials.

3         DR. SMITH:  So I would like to summarize

4    very briefly, perhaps not inclusively, on the

5    discussion we've just had.  And so what I heard was

6    expressions of concern in regard to the various

7    issues such as changes in protocol, endpoint

8    definitions, analysis plan as posed in this

9    discussion by the -- for this question by the FDA,

10   that that presents concerns and issues in terms of

11   interpretation of the data.

12        A couple members of the committee expressed

13   a high level, or a pretty high level, of confidence

14   in the conclusion that excess cardiovascular risk

15   was excluded, and that wasn't opposed by comments

16   from other members of the committee.

17        In regard to cardiovascular benefit, there

18   was a lot of discussion.  There's substantial

19   concern expressed by various members of the

20   committee.  One of the points that was raised was

21   that the fact that there's some uncertainty in

22   regard to the MACE 3 primary outcome raises some

1   fundamental questions about the amount of emphasis

2   that should be placed in interpreting the

3   cardiovascular mortality data.  That was not a

4   universally expressed opinion.  There was

5   controversy on that from within the committee.

6        Certainly, there were comments made on the

7   importance clinically and the clarity of definition

8   of mortality, all-cause or cardiovascular

9   mortality.  There were issues raised about the non-

10  assigned deaths that then ended up as presumed

11  cardiovascular mortality.  That's an issue, but it

12  was noted that, in that regard, that all-cause

13  mortality still upholds significance, and that was

14  somewhat reassuring.

15       Another point that was made, which is one of

16  the overriding issues that adds to some of the

17  difficulty of interpreting these data, is that we

18  haven't been presented with a plausible mechanism

19  for the effects of this drug on cardiovascular

20  mortality.

21       So that's my summary.  Did I leave out

22  anything critical that people would like to state?

1          (No response.)

2          DR. SMITH:  I think we'll move to discussion

3     question 2.

4          Dr. Rosenberg, you had a comment?

5          DR. ROSENBERG:  Yes, just a slight

6     modification on your last point.  The mechanism of

7     action may probably not on atherosclerosis because

8     it's very early and we don't have a clear

9     explanation of this early benefit.

10          DR. GUETTIER:  Can I get just a little bit

11    more clarification, Dr. Smith?  It's Jean-Marc from

12    the FDA.  So this trial, to some extent, was a

13    child of the 2008 guidance and a lot of the issues,

14    at least in the conduct that we sort of came about,

15    came out because actually this is really a safety

16    trial.

17          I think I heard sort of at least the

18    specific discussion point was really focused on

19    whether or not what we presented this morning in

20    terms of the changes.  What is your level of worry

21    about the quality of the data that comes out of

22    this trial?  A lot of the discussion, actually,

1    from this discussion point, were more towards

2    discussion point 2 and 3, but in terms of the level

3    we heard from Dr. Konstam, I was wondering if

4    anyone else had any other comments on that.

5         DR. SMITH:  Would anyone like to respond to

6    that?  Yes, Dr. Rosenberg?

7         DR. ROSENBERG:  I think I have no concern

8    about safety.

9         DR. EVERETT:  I'll answer.

10        DR. SMITH:  Dr. Everett, I got the wrong

11   person there.

12        DR. EVERETT:  My confidence in the mortality

13   data is reasonably high.  My confidence in some of

14   the other endpoints, myocardial infarction and

15   heart failure in particular, is much lower.  And

16   I'd be very wary about -- because of the design

17   issues we've discussed, we haven't really even

18   addressed the heart failure issues at length yet in

19   this discussion, but that would be my short answer

20   to your question.

21        DR. SMITH:  I might give a longer answer,

22   which is that I -- so the 2008 guidance includes

1    within it language that focuses on MACE or a

2    MACE-plus.  And when we look at those specific

3    endpoints that were within the 2008 guidance, and

4    then if we look at an extension to an efficacy

5    trial, we obviously encountered some uncertainty

6    with the data within this study.

7    Depending on how we choose to analyze,

8    include, or exclude in terms of the analyses of

9    some of these factors that were raised as concern,

10    not only MACE 4 but MACE 3 comes under question.

11    So if we simply look at the simple extension of the

12    2008 guidance into an efficacy superiority trial

13    rather than a non-inferiority trial, we have

14    encountered some issues in the context of this

15    study.

16    We happen to have had another event happen

17    here, which is that we have this rather dramatic

18    cardiovascular mortality data.  And in a way it's

19    sort of on and off topic to me in terms of your

20    question because that's a component of a MACE, but

21    instructions aren't clear from that 2008 guidance.

22    So I think there are complexities in trying

1     to move from a guidance that was generated to help

2     in the design of studies with a primary goal of

3     establishing safety to something that is looking at

4     superiority, and we've encountered some of those

5     difficulties.  I don't know if that's helpful.

6          Yes?

7          DR. KEWALRAMANI:  From the perspective of

8     the design of trials, whether the original intent

9     was the exclusion of the hazard ratio of 1.8 or

10    1.3, or the construct of such a trial for

11    superiority over standard of care, I think that the

12    study here was powered.  While there were changes,

13    these changes were made apparent.

14         There was a CEC involved, and I think

15    whether or not silent ischemia was in or should

16    have been in, whether it was designed as a safety

17    study or efficacy study, that would have been the

18    same.  And the non-assessable -- I think, while the

19    numbers may be higher than we would like, I don't

20    think that that is a function, per se, of safety

21    study for the exclusion of a 1.3 or 1.8 or for the

22    demonstration of superiority.

1          So I think if we really look under the hood

2     of this study, it would look like a study that we

3     would design for the purposes of demonstration of

4     cardiovascular morbidity and mortality.

5          DR. SMITH:  So, I would like to move to

6     discussion question 2.  I'll read this.  Please

7     discuss the persuasiveness of the statistical

8     results for the primary analysis.  Please also

9     comment on how results for the individual

10    components in the primary composite endpoint impact

11    your level of confidence in the study findings.

12         Finally, comment on concerns you may have

13    related to potentially incomplete ascertainment of

14    some myocardial infarction events, i.e. silent MI,

15    in this trial, and whether these concerns, if any,

16    alter your level of confidence in the results for

17    the primary analysis.

18         So we've obviously in part discussed this,

19    but let's briefly at least revisit those issues.

20    Yes, Dr. Hiatt?

21         DR. HIATT:  I thought a little bit more

22    clearly I think in terms of trying to frame the

1    issue.  So you come into this with a guidance and

2    the idea that we're trying to exclude the risk of

3    MACE and now show that we have superiority on MACE.

4    And if you think about the history around that,

5    around drug trials using anti-thrombotic agents or

6    statins, really what drives that historically is a

7    reduction in fatal and non-fatal myocardial

8    infarction.

9         That's how you sort of come into this.  And

10   when you then go back to the primary MACE endpoint,

11   which is on a single pivotal, not very convincing,

12   and then look at a couple of other analyses, MACE

13   on-treatment, which should be a little stronger,

14   has an upper bound of 1.02, MACE-plus silent MI,

15   upper bound of 1.06.

16        Fatal and non-fatal MI, you know the thing

17   that you think would drive it, has an upper bound

18   of 1.09.  And there's no benefit on stroke,

19   combined with the idea that I think we get to CV

20   death as a post hoc exploratory analysis.  So

21   that's the problem I'm having with this.

22        So in some ways, I think, Michael, you've

described this, you sort of have to sort of set all

that aside and say it's just CV mortality, that's

it.  And I don't know if there's a mediation

analysis or something looking at what's driving

that.  I just don't think we have a clue.

It doesn't look like it's the kind of

mechanisms that most cardiovascular outcome trials

are designed to test, which is plaque rupture and

thrombosis.  I don't think it's that.  It might

have something to do with that, but it's driving

mortality down for some other reason.

I think that's where my discomfort with

trying to wrestle with what to do here, is really

strong because starting out this discussion, I

couldn't get to CV mortality very easily because

you went on MACE and then there's nothing beyond

that that really logically takes you to a

hierarchal analysis to move into the components.

But you sort of say you're just being awfully

technical, and sort of acting like what I learned

from you guys, Norm and Bob, on cardio renal, so

I'm a little hung up on this point.

1          But that's the problem here.  Because it's

2     mortality, you said what the heck?  Just throw all

3     that other stuff out and it's just death, and

4     nothing else really matters.  But then, if that

5     were confirmed by another agent in the class, say,

6     wow, there's something going on here, and maybe

7     we'll be smarter in five years and figure out what

8     the mechanism is and say we should have thought

9     about that, but it certainly makes sense.

10          The history of statins were sort of getting

11    on the market because they changed a surrogate.

12    And then suddenly, they show cardiovascular benefit

13    later and things came together.  So there's

14    precedent for that.  But I think the statistical

15    part of this is weak.  I just don't think it gets

16    me to this single-component analysis.

17          In that regard, I'm sort of left with just

18    saying, I don't know, I'm not convinced, but

19    there's a CV mortality.  And it's just hard to kind

20    of get your arms around that in some rational way.

21          DR. SMITH:  Dr. Neaton?

22          DR. NEATON:  Let me just ask a question

1    about the history and the focus on MI.  So my

2    history and trying to discern whether a person died

3    from fatal MI or sudden death, that's very hard.

4    So they've actually classified the deaths by fatal

5    MI, so when they look at fatal versus non-fatal MI,

6    I'm assuming that's what they're using, that

7    classification.

8         But presumably there are sudden deaths in

9    these not accessible deaths that are being judged

10   cardiovascular that would probably fall into that

11   category.  I mean, the fatal/non-fatal MI results

12   are trending in the right direction at least, the

13   same as the overall outcome.  So I think the

14   overall -- my summary of this is that you're on a

15   very fragile area for the primary MACE outcome.

16        I don't know, Marv, how I would react if it

17   was 0.06 or 0.07 versus 0.03.  I think the range of

18   p-values we're seeing is somewhere in the range of

19   maybe 0.02 to 0.10, based on the various

20   sensitivity analyses.  But it's being driven by an

21   outcome that really makes a difference.  And every

22   way you look at that outcome, it adds up as having

1    an impact on mortality.

2         So I don't think you can ignore it is the

3    way I think about it.  And you should view these

4    p-values as giving you some strength of the

5    evidence and not getting locked in on the magic

6    0.05.

7         DR. SMITH:  Dr. Konstam?

8         DR. KONSTAM:  Well, first of all, everybody

9    I listen to changes my mind.

10        (Laughter.)

11        DR. KONSTAM:  So be careful what you say.

12   But just as a point, I want to sort of go after

13   this point about, well, this is mortality.  This is

14   really important.

15        I think the question in front of us is do we

16   believe the finding.  I mean, that's the question.

17   It is not this is a really important finding,

18   therefore we ought to believe it.  I mean, that's

19   backwards.  Right?  We ought to first decide do we

20   believe it, and then we decide that it's important.

21        I think that the issue around, when we get

22   to it, about the cardiovascular mortality -- so

1    first, let me just say, this is a drug that's

2    already approved.  Okay?  There's a paper in the

3    New England Journal about this that says that the

4    drug reduces mortality.  So we're not talking about

5    approving the drug or not approving the drug.  It's

6    already in the academic literature that that's what

7    it does.  It reduces mortality.

8         The question here is, is the FDA going to

9    approve it for that indication, for that goal.  And

10   the way I think the FDA thinks about this in its

11   core is, do I believe the finding or not.  Is this

12   something that we agree with so strongly that we're

13   going to say to the prescribing public this drug

14   reduces cardiovascular mortality?  So I think that

15   discussion is independent of this is a really

16   important endpoint, to me.

17        DR. SMITH:  Dr. Budnitz?

18        DR. BUDNITZ:  I was going to add that the

19   statistical analyses that most intrigued me was

20   actually the on-treatment analyses, which seemed to

21   make no difference for the endpoints in MACE of MI,

22   and if I'm recalling, I think stroke.  But where

1    they did make a difference, and I think the about

2    25 percent discontinuation rate, so I would expect

3    there would be more efficacy for the on-treatment

4    subgroup.

5         It did show up for cardiovascular mortality,

6    where the overall rate of hazard ratio I think was,

7    for example, on the order of 0.66.  But on

8    treatment, it was 0.52.  So for me, that was

9    reassuring that this drug might do something, and

10   it was notable that the on-treatment results were

11   completely the same for the other MACE endpoints.

12        DR. SMITH:  Dr. Schambelan?

13        DR. SCHAMBELAN:  I just wanted to add, I did

14   look up the data for LIFE and the p-value was

15   0.021, but the point estimate was almost identical

16   to what -- this is for the MACE outcome -- was I

17   think 0.85 or 0.86, very similar to what we saw

18   here.  So I don't know, Marv, how you feel about

19   going from 0.02 to 0.04 to 0.07.

20        DR. KONSTAM:  I don't know.

21        (Laughter.)

22        DR. KONSTAM:  I think -- like I'm trying to

1   be rigorous with what I've learned from the FDA

2   over the years they want.  Right?  That's all.  And

3   what they want is two studies.  And if they don't

4   have two studies, they want to feel good that they

5   still have the right answer.  And one of the

6   important things they look at is how low is the

7   p-value.

8         So, I just ask the question, if the p-value

9   of the primary isn't that low, how do you know it's

10  right, okay, with a single trial, and does that

11  affect your willingness to approve it for a

12  component of the primary endpoint.  That's what

13  they did.  Maybe they need to explain themselves,

14  but that's what the issue is.

15        DR. SMITH:  Further discussion on this

16  point?  Yes?

17        DR. YANOVSKI:  So I'm really struck by the

18  fact that the evidence I'm hearing doesn't seem

19  like this is driven by a reduction in

20  atherosclerotic cardiovascular disease in terms of

21  the reduction in those MACE components, in terms of

22  the timeline.  We don't really know the mechanism,

1    but where you're really having your bang for the

2    buck is in this really robust reduction in

3    cardiovascular mortality.

4         I was reassured by the fact that even when

5    you did the sensitivity analysis, not looking at

6    those where you couldn't really -- where you didn't

7    know if it was cardiovascular or not, it didn't

8    really change your findings.  So everything I'm

9    hearing tells me that this is a real finding.  We

10   don't really know why.  We don't know the

11   mechanism.  Do we need to know the mechanism to

12   approve the indication?  I guess that's the

13   question.

14        DR. SMITH:  Dr. De Lemos?

15        DR. DE LEMOS:  Yes.  I think just to

16   summarize, there's some excellent points.  I think

17   that I'm more persuaded by a weak p-value for the

18   primary endpoint and a really robust p-value for

19   the mortality endpoints than I would be for two P

20   0.02s for both.  I think that's what -- some people

21   would be happier with that result in terms of

22   allowing the drug to get a cardiovascular

1    indication.

2         I'm also very favorably influenced by the

3    multitude of influences on blood pressure and

4    favorable influences on renal function and heart

5    failure that, while by no means conclusive and

6    terribly limited, all line up in the right

7    direction.  The non-fatal effects on myocardial

8    infarction -- with the exception of stroke,

9    everything lines up in the right direction to

10   support a cardiovascular mortality benefit that's

11   favorable.

12        It's not conclusive, but then what's really

13   buttressed is the all-cause mortality.  It's not

14   going to be the indication, but as Brendan said, I

15   think that's what gives you -- that markedly

16   increases my confidence in the CV mortality

17   finding.

18        DR. SMITH:  Yes, Dr. Good?

19        DR. GOOD:  Yes, since stroke was just

20   mentioned here by my colleague, perhaps we should

21   talk about that just for a minute.  I think the

22   most important thing is that there wasn't any

1    statistically significant difference in HR between

2    the treatment groups and the placebo, and that's a

3    fact.

4         I think there's a very soft signal that

5    perhaps there's a slightly higher risk of stroke,

6    but I think the point is that it was across the

7    board, across all stroke pathophysiologies was

8    pretty interesting.  It's lacunar stroke, it's

9    cardioembolic stroke, it's atherosclerotic stroke.

10   Maybe that kind of feeds into this mechanism issue

11   as well.

12        I have a little bit of concern about whether

13   there is a regional difference in diagnosis of

14   stroke.  I have no idea why the stroke incidence

15   was higher in Europe than it was in other areas,

16   and the sponsors had no idea either.  I'm not quite

17   sure what to do with that.

18        Regarding the TIA issue, a TI is usually

19   considered in the same category as ischemic stroke.

20   It's a little bit harder to diagnose because there

21   are many causes of TIAs.  They're not always

22   ischemic stroke.  I'm not sure about rolling that

1    in with ischemic stroke and looking at then how

2    that changes the HR, whether that's really legit or

3    not.

4         I think in the end, I'm not terribly

5    concerned about the stroke, the non-fatal stroke.

6    I do think that there's a little signal we have to

7    think about, but I don't think we should focus

8    extensively on that point.

9         DR. SMITH:  Yes, Dr. Fradkin?

10        DR. FRADKIN:  Thanks.  I agree with Dr.

11   Yanovski that the fact that we don't know the

12   mechanism shouldn't be a reason not to approve it.

13   Clearly, it's something different than

14   atherosclerosis just based on the time course,

15   based on the fact that we started to see the lines

16   diverge from the very beginning.  I think we would

17   have to be looking at some other mechanism,

18   something about survival of an MI rather than

19   atherosclerosis.

20        To me the entire issue though boils down to

21   whether when it's one of multiple secondary

22   endpoints, are we sure, based on the fact that the

1    death, robust as it looks, is a secondary endpoint.

2    Can you approve it with one trial?  And that to me

3    is the crux of the question.

4        DR. SMITH:  Anyone have a specific comment

5    in regard to a component of this discussion point

6    in terms of the silent MI?  We've already talked

7    about this extensively, but any further comment

8    that anyone -- Dr. Hiatt?

9        DR. HIATT:  Yes, I sort of added that in my

10   earlier comments.  But I think there are a number

11   of things that make the p-value dance around 0.05

12   for the MACE primary, and that's all it does.  I

13   think we talked a lot about it earlier that it's

14   probably not reliable.  It's probably mostly noise.

15       But, you know, the on-treatment analysis

16   takes it to non-significant, and the

17   fatal/non-fatal MIs are not significant.  So I

18   think it's all kind of telling us that this is not

19   having a profound effect on ischemia per se, it's

20   probably something else.  And that's all I've

21   learned from that discussion.  I don't think it's a

22   fatal flaw.

1          DR. SMITH:  Yes, Dr. Proschan?

2          DR. PROSCHAN:  Yes.  I absolutely agree that

3  the evidence for MACE 3 is not that strong and you

4  don't have to do much to tip it the other way.  And

5  I am aware of the fact that there have been other

6  trials where you see a very small p-value on a

7  secondary endpoint, you try and repeat it, you

8  can't repeat it.

9          Again, my explanation for that is that there

10  is a lot more multiplicity than you think.  If you

11  had seen that the 10-milligram dose had shown a

12  really strong benefit, you would have emphasized

13  that.  So there's a whole lot more multiplicity

14  than you think.

15          However, I still believe that, based on the

16  evidence that we've seen, that the mortality

17  finding, cardiovascular mortality is real.  Now is

18  this estimate of the hazard ratio biased?

19  Absolutely, yes it is.  So it's not going to be as

20  strong as what's indicated here.  I feel pretty

21  confident about that.  But I do also feel pretty

22  confident that it's not a hazard ratio of 1, it's

1    less.

2           DR. SMITH:  Dr. Rosenberg?

3           DR. ROSENBERG:  I would slightly disagree

4    with Dr. Fradkin.  When we're talking about a

5    secondary endpoint that is strongly positive like

6    it is observed, you really would like to have a

7    mechanism to understand why it's such.  That's the

8    only thing I would add.

9           DR. SMITH:  So I might summarize that in

10   responding to this question, we a little bit

11   tracked over the same set of opinions and views

12   that have been presented with the first discussion

13   question, which is that there is concern or

14   uncertainty about the primary combined MACE

15   endpoint.  And that's affected by a number of

16   variables, including looking at the individual

17   components of that, which further highlight the

18   issue that we don't really understand the mechanism

19   of the effect on mortality.

20          Again, we heard a divergence of opinions

21   from the committee in terms of the mortality data.

22   And that is not so much questioning what those data

1    are, but the actual strength of that as a single

2    study result.  And I think with a greater

3    acceptance of that as a strong indicator of benefit

4    by some members of the committee and much stronger

5    expressions of uncertainty about other members of

6    the committee as to whether that in fact would be

7    reproduced in a second trial.

8         Anyone want to add anything, or FDA settle

9    for a quick summary on that point?

10        (No response.)

11        DR. SMITH:  So we'll go to the next

12   discussion question.  Again, we've covered some of

13   these points, but this I think will bring back some

14   emphasis on others.  Discuss the persuasiveness of

15   the mortality findings in the EMPA-REG OUTCOME

16   study.

17        In your discussion, please address any

18   potential limitations of these data, including but

19   not limited to issues raised in discussion point

20   number 2, the proportion of deaths that were

21   determined non-assessable by adjudicators, the lack

22   of granular data on potentially important

1    information such as baseline heart failure history

2    and dose of relevant baseline and concomitant

3    medications, and the lack of prespecified alpha

4    adjustment for this endpoint.

5            So I'll open that for comment.  Yes,

6    Dr. Konstam?

7            DR. KONSTAM:  Actually, I have new

8    information to bring to the group, okay, because

9    I've been working here.  So with regard to this

10   question, most of my focus has been on lack of

11   prespecified alpha adjustment for this endpoint,

12   and I think there's really concern about that.

13   Now, I want to say something, a few things on the

14   positive side.

15           There are things about this that drive you

16   toward -- help me get a little bit more comfortable

17   that this is a real finding.  One is the very low

18   p-value.  The second is the number of events, okay,

19   and I'll get back to that in a second, 309 events.

20   I'm focusing on the cardiovascular death endpoint,

21   so 309 events.

22           I'm also influenced by the fact that you

could argue there's sort of two trials in here

because there are two different doses, and both of

those doses show the same thing.  So that actually

is the one piece of information in the dataset that

moves me along in thinking about this.

I looked up three trials where there was

something like this, that is, there was a mortality

endpoint that jumped up and wasn't expected either

because it wasn't the primary, it was a subset

analysis, some secondary analysis or something.

The first one was PRAISE with amlodipine.

And the finding was that in dilated cardiomyopathy

patients as opposed to ischemic heart disease

patients, it reduced mortality.  That finding was

not confirmed subsequently with a larger trial.

In that trial, the first one, the PRAISE

trial, there were a total of 103 events compared to

what we have here, which 309 events.  It was

associated with a pretty low p-value.  They just

quoted as less than 0.001, so the p-value didn't

help very much, but maybe the fact that it was a

third as many events may influence us.

1          The second one is with losartan against

2     captopril.  There was an ELITE trial for which the

3     primary endpoint focused on renal function

4     comparing captopril and losartan, but a mortality

5     benefit for losartan popped out of nowhere.

6          So there, first of all -- by the way, in

7     both of these trials, in the first PRAISE trial and

8     in the ELITE trial that I'm mentioning, the primary

9     endpoint was non-significant.  Okay?  That's

10    another point.  But this finding with losartan

11    versus captopril was not replicated in ELITE II.

12    In ELITE, the p-value was only 0.035, and there

13    were only 49 events.

14          The third example is the carvedilol trials

15    in the mid-90s where there was a huge amount of

16    controversy about whether the mortality data should

17    go into labeling for the drug because the finding

18    was a composite of four different trials, none of

19    which was designed to look at mortality.  That one

20    was approved after a second panel with 53 events.

21    Why was that approved?

22          (Laughter.)

1          DR. KONSTAM:  Fifty-three events and a

2     p-value of less than 0.001.  And then, actually,

3     Bob mentioned the LIFE study.  Well, that's

4     different because it didn't show mortality benefit.

5     I won't talk about that.

6          My take home out of this is that if you look

7     at all of the information in those three trials,

8     none of them were as robust as what we've got in

9     terms of both the p-value and the number of events.

10    So I think those compared to these other findings

11    that turned out not to be true looks a little

12    stronger.

13         DR. SMITH:  Any other discussion of this

14    question?  Dr. Thomas?

15         DR. THOMAS:  First, I just wanted to echo

16    what Dr. Cho mentioned, which is, at least in the

17    United States, I don't know about the rest of the

18    world, with observation status being required by

19    Medicare, and many insurers also having that, you

20    have to include those patients, even if they're not

21    hospitalized because you're very unlikely to get a

22    straightforward heart failure patient being

1    admitted nowadays in a hospital that has

2    observation care because they can only get

3    readmissions.  And with the new insurance rules,

4    you won't be able to get them hospitalized.

5          So it is something probably future trials

6    will have to look at because otherwise, if you just

7    go by hospitalizations, you're going to miss all

8    these cases.

9          That's an important point and it addresses

10    this heart failure issue.  This wasn't set up to be

11    a heart failure trial, so in a way it doesn't

12    completely matter if all the data is not as

13    complete or rigorous as it would be in a heart

14    failure trial.  All the other cardiovascular

15    information is more persuasive in terms of

16    cardiovascular death.

17          Then the last thing is we don't have a

18    mechanism.  But if you think about mechanisms, not

19    glucose, because with glucose, we've had large

20    trials that have not shown glucose to work,

21    atherosclerotic is unlikely.  It's so quick.

22    Right?  Blood pressure, it had a blood pressure

1　　effect, but it's still pretty quick.  We should see

2　　similar effects of blood pressure agents.

3　　　　　　One thing we've been skirting around -- and

4　　I think the reason I bring this up is hopefully, if

5　　there is a trial that's done or other analysis

6　　probably needs to be looked at, is we've been

7　　mentioning the word dead in bed a lot.  And that

8　　usually relates to people who have autonomic

9　　neuropathy, poor RR variability, and that's not

10　　something that was probably looked at in this trial

11　　but is something we probably should address.

12　　　　　　Is there some effect of these agents on

13　　autonomic neuropathy or some other surrogate that

14　　is having an impact on sudden death or arrhythmias?

15　　We won't need the mechanism right now; shouldn't

16　　preclude us from approving something or not

17　　approving something because, you know, aspirin was

18　　around for 80 years without a mechanism.

19　　　　　　DR. SMITH:  Dr. Budnitz?

20　　　　　　DR. BUDNITZ:  I think the concern I have

21　　about the mortality finding relates to the third

22　　bullet there, the lack of granular data on

1    potentially important information based on heart

2    failure and concomitant medications, particularly

3    because so much of the data come from outside the

4    U.S., like 80 percent outside North America.  And

5    we just don't know what the -- or at least I don't

6    know what the treatment and baseline

7    characteristics of these folks are, whether it's

8    diet, whether it's the dose and duration of other

9    medications, particularly when we don't have a

10   mechanism.

11           So it's not an issue of statistical

12   interaction.  It's an issue of generalizability

13   where I'm not quite sure what these folks look

14   like, if they look like the patients that are being

15   treated in the U.S..  And so this lack of

16   information about if the mechanism is some sort of

17   hemodynamic and heart failure mechanism, we don't

18   have information about what medicines folks are

19   taking for heart failure and their baseline echoes

20   or other characteristics.

21           DR. EVERETT:  Dan, could I just ask you a

22   follow-up?  Are you worried that the randomization,

1   that those issues are not balanced on either side

2   of the randomization?  Or what are you worried

3   about?  Because to me, that's a concern in terms of

4   defining mechanism, but you have a randomized

5   trial, so theoretically at least, they should be

6   balanced.

7           DR. BUDNITZ:  Right.  And so it's not that

8   there's no effect, but the magnitude of the

9   difference.  So for example in Asia, the hazard

10  ratio was 0.3.  In the U.S., it was 0.8 for

11  cardiovascular mortality.  So you can do a test for

12  interaction, and that can be negative, but

13  clinically I think that might be different.  And so

14  I do think that there's the potential for there to

15  be differences by region.  Does that make sense?

16          DR. SMITH:  Dr. Proschan?

17          DR. PROSCHAN:  Not to throw another

18  statistical issue in, but people have talked about

19  trying to repeat a result and you don't get the

20  result the second time.  That's not necessarily

21  saying that it wasn't true, right, because you have

22  two trials.  One says there's something going on,

the other one says there's nothing going on.  You

don't know what the right answer is still.

Moreover, when you do the second trial, what

people usually do is they say let's assume the

treatment effect that we saw in that last trial,

and let's power it for that.  That treatment effect

is going to be biased because you did notice that

because it was a secondary outcome, and, wow, look

at this.  So that treatment effect is almost surely

going to be too strong.  That's not really what the

true effect is.  So really, you should take that

into consideration.

Then, when we stupidly a lot of times power

trials for 80 percent, which means even if you're

correct that the treatment effect was what you saw

last time, you have a 1 in 5 chance of not getting

a significant result.  So the fact that another

trial didn't confirm it doesn't really tell you

that it's not true.

DR. SMITH:  Dr. Palevsky?

DR. PALEVSKY:  A couple thoughts.  As a

trialist, we use composite endpoints because we

1    don't think that any one of the individual

2    endpoints in the composite is going to have a high

3    enough event rate for us to have a significant

4    outcome with a trial that is going to be feasible

5    to conduct.

6         If we were to ask a patient what's important

7    and ask them the hierarchy of the endpoints in the

8    composite in either MACE or MACE 4, I think I'm

9    just going to speculate that they'd put mortality

10   at the top of that list and take non-fatal events

11   as of lower importance.

12        So although I have concern over the fact

13   that the mortality is moving in a different

14   direction from the overall composite, which may or

15   may not have quite reached the p-value of 0.05, I

16   am quite impressed by that.  I don't think that the

17   sponsor would have dared propose a trial just

18   looking at cardiovascular mortality.

19        That said, I am a little bothered by the

20   lack of the mechanism.  And one concern, not so

21   much the difference in the co-management at

22   baseline, but could there be some effect of

1    interventions after the patient's on trial, either

2    alternate management of glycemic control that may

3    have diverged because this is a hypoglycemic agent

4    and what are the co-management?  Or diuretic

5    management since it does have a diuretic effect?

6         One of the questions that I have is, what

7    were the impacts of the co-management on the trial

8    on this mortality outcome?  And could we be missing

9    something that it may not be entirely the benefit

10   of this agent, but a mixture of benefit of this

11   agent and some detriment to the co-management that

12   was occurring?

13        DR. SMITH:  Yes, I think that's an

14   interesting comment.  And just to sort of expand on

15   that a little bit what some of those factors

16   potentially might include would be the difference

17   in hemoglobin A1c, which was modest, somewhere in

18   the range of 0.5 percent, plus or minus difference,

19   depending on how you choose to look at the data.

20        There was a difference in blood pressure

21   that again was only a few millimeters of mercury,

22   but it went in a direction downward, which one

1    might think would be favorable.  And there was a

2    difference in additional medications used to manage

3    glycemia, even though the glycemia wasn't as

4    effectively managed so there was more insulin and

5    there were more sulfonylureas.

6         I find it difficult to focus on any one of

7    those, and not even particularly comfortable to

8    pool them all together and say, "Ah ha, there's the

9    explanation."  But the fact is they do again add a

10   little discomfort.  It's another version of the

11   mechanism argument.  It adds a little discomfort to

12   the strength to place on the mortality data

13   themselves.  Dr. Thomas, you had a comment?

14        DR. THOMAS:  So I think those are all

15   important points.  Actually, when the guidance

16   first came out and the way these trials are

17   designed, physicians have the judgment in these

18   trials to adjust medications as they feel fit.

19        There's no predefined protocol as in other

20   trials.  So, for example, in most trials like

21   ACCORD, you had a target.  So if you blood pressure

22   didn't hit that target, you had to do something,

1   either to increase the medication, you just

2   couldn't sit as is.

3          Here, there is no guidance.  You just do

4   what's the norm for your community.  So the fact

5   that actually anything shows up amongst all this

6   noise of treatment is to me actually quite

7   astounding.

8          I actually was very surprised that anything

9   would show up in these trials beyond

10  non-inferiority because there's so much noise in

11  the management.  Someone could up the statins,

12  someone could not up the statins.  They're not

13  treating towards our guidelines or treatment.  They

14  should, but there's nothing requiring anyone in any

15  of these management of the patients, to do anything

16  other than give the placebo or the drug.

17         DR. SMITH:  Dr. Li-Ng?

18         DR. LI-NG:  I just wanted to point out my

19  general concern about the indication that's been

20  sought by the sponsor.  The SGLT2 inhibitors are a

21  relatively new class of medications that have been

22  added to our diabetes treatment regimen.

1          In regards to some of the studies that Dr.

2     Konstam had brought up, there were other studies

3     that showed some benefit in terms of ACE inhibitors

4     or ARBs or beta blockers to add the indication for

5     cardiovascular event prevention.

6          My concern is that given this one study

7     again showing very persuasive evidence that there

8     is a decrease in cardiovascular mortality and all-

9     cause mortality, I can't -- again, my concern is

10    that this is one study in a new class of

11    medications and we haven't seen any other studies

12    showing the same thing.

13         DR. SMITH:  So what I would like to do is

14    summarize what's been said so far, and any critical

15    additional comments can be made.  I'm anxious to

16    move us along because we have two more discussion

17    questions and two voting questions and I don't want

18    to be rushed at the end here.

19         So in regard to this discussion question,

20    again, we've a little reiterated some of the same

21    issues.  We've heard some arguments about the

22    persuasiveness of the mortality data in terms of

the very low p-value itself, the substantial number

of events in this trial, particularly in comparison

with several historical trials, and the fact that

the two doses of the drug showed really very

similar effects on the mortality endpoint.

We, again, members of the committee

expressed concern about a non-understanding of

mechanism.  And the suggestion was made in regard

to potential effect on autonomic nervous system and

the relationship between disturbed autonomic

signaling and sudden death.

But also the point was made that it may not

be essential to know the mechanism in order to

place strength in the mortality data.  And in that

same context, the point was made that among all the

elements of the composite endpoint, the one that

clinically certainly would be viewed as being the

most important is the mortality data itself.

Again, in regard to how the FDA may consider

responding to these mortality data, the point was

made that this does represent the first member of a

drug class.  So again, it's another version of

1    being a single study, one might say.  I don't want

2    to open a bag of worms with that comment.

3           Any other comments before we move on?  So

4    let's go to the next discussion question.  And I

5    don't want to short-change any of these questions,

6    but I'd like us to try to be a little bit brief so

7    we have adequate time to deal with the voting

8    questions.

9           So this question, number 4, discuss the

10   heart failure findings in the EMPA-REG OUTCOME

11   study.  Please comment on the potential limitations

12   of these data, if any, and on whether the results

13   of this study establish a benefit of empagliflozin

14   on heart failure and heart-failure-related

15   outcomes.  Yes, Dr. Konstam?

16          DR. KONSTAM:  This one, I have a bigger

17   problem with.  Okay?  So it's nowhere to be found

18   in the hierarchal testing.  It's not a component of

19   the primary endpoint.  The p-value is not as

20   impressive.  So as has been said, you really have

21   no idea what it really is.  It's nominally 0.0017,

22   but given the multiplicity involved here, it's

1   really undeterminable.  And for what it's worth,

2   it's not death.

3        I'd like it to be true.  I kind of think it

4   probably is, but it doesn't reach my standard of

5   provability.

6        DR. SMITH:  I'll try Dr. Thomas.

7        DR. THOMAS:  I would just add to that and

8   then FDA can correct me if I'm wrong.  If this was

9   being done as a heart failure study, this agent

10  would have to be an add-on to currently approved

11  standard of care.  We have no idea what was really

12  being done throughout this trial.  So it's an

13  intriguing finding, and if it really needs to be

14  explored, it probably needs to be explored in a

15  different study that's formally done for heart

16  failure.

17       DR. SMITH:  Dr. Everett?

18       DR. EVERETT:  I just want to preface my

19  comments with the fact that heart failure is a very

20  prevalent problem.  It's an important problem.

21  It's increasingly important.  And to echo Dr. Cho's

22  comments earlier about a shift in the way that

1    these patients are managed from hospitalization, to

2    outpatient treatment units, to potentially

3    even -- I have an email in my inbox about a

4    randomized trial of treating them at home.  So

5    there's a lot of impetus to try and treat these

6    patients outside of the typical healthcare setting,

7    so it's an important endpoint.

8         But, when you have a definition that shifts

9    over the course of the trial and is not anywhere

10   near close to the primary endpoint, to echo Marv's

11   points, or a component of the primary endpoint, my

12   willingness to accept these results a priori, I

13   think, without the benefit of a second heart

14   failure-focused trial where done by investigators

15   practiced in the art of doing those trials, which

16   are very challenging, I'm reluctant to accept the

17   results at face value.

18        DR. SMITH:  Other comments?  Yes, Dr.

19   Palevsky?

20        DR. PALEVSKY:  So I will echo the comments

21   about the rigor.  And just another point to

22   remember, this is an agent that is a diuretic as

1    one of its mechanisms of action.  And we just need

2    to bear that in mind that it's going to have an

3    effect on volume management that may not have

4    been -- you know, basically the patient was on a

5    higher dose diuretic than otherwise considered.

6    I'm not very impressed by the heart failure data.

7            DR. SMITH:  Dr. Wilson?

8            DR. WILSON:  Just a follow-up.  I think we

9    lack modern metrics, and we need some new metrics

10    for this.  And perhaps, for instance the person who

11    goes into the ED observation unit and goes home,

12    that's one hospital day, if that, versus those on

13    the wards, we have hospital days, D-A-Y-S, plural.

14            So that's another thing to think forward,

15    because this is going to keep coming back to these

16    sorts of committees, what is the heart failure

17    metric in 2017, 2018, 2019.  So one of them is

18    days.  The other is major changes in outpatient

19    doses.  But I still go back to some sort of symptom

20    complex and weight loss with the diuresis over a

21    short term.  We need better metrics for evaluation

22    of this outcome moving forward.

1          DR. SMITH:  Yes?  Dr. Proschan?

2          DR. PROSCHAN:  So I agree that I think the

3    results are not nearly as compelling for heart

4    failure.  But I also wonder why is this even a

5    question if they are no longer asking for that,

6    anything to be said about heart failure.

7          (Laughter.)

8          DR. SMITH:  Well, I think the FDA poses

9    these discussion questions not limited to a

10   specific indication that may be under

11   consideration, but something that may help to

12   inform them in a background way for that decision,

13   but also in terms of future issues.  This is a drug

14   where there may be a future heart failure study,

15   for example.  So I don't think they're restricted

16   to working around their indication request.

17   Dr. Rosenberg?

18         DR. ROSENBERG:  So maybe I'm old fashioned,

19   but a change in class of heart failure is something

20   that we used to look at and we don't even have

21   baseline here, so it's hard to say anything.

22         DR. SMITH:  Dr. Cho?

1      DR. CHO:  I just want to reiterate that this

2    is clearly not a heart failure trial and they

3    didn't even have New York Heart class association

4    as part of the trial.  But I just want to -- I

5    mean, it's a very interesting finding, and I want

6    to encourage the Boehringer Ingelheim group to

7    study it in the heart failure patient population

8    because it would be so interesting to look at it in

9    that particular population.

10      DR. SMITH:  To summarize what's been said so

11   far here, committee members have expressed the view

12   that this is an important clinical endpoint.  I'll

13   add to that, we haven't talked in detail here in

14   this discussion about the prevalence of heart

15   failure within type 2 diabetes, but it's high and

16   it's clinically significant.  It's limiting

17   clinically to people who have heart failure

18   functionally.  It's limiting.  So it's an important

19   endpoint.

20      It's been noted that these data are quite

21   intriguing, and so I suppose we can interpret that

22   if in fact a beneficial effect on heart failure

1   were adequately substantiated, that would be an

2   important effect of the drug.

3           The point was noted that this drug has

4   diuretic properties.  So in that context, one would

5   want to know whether they were using a diuretic and

6   whether there were alternative diuretics or whether

7   this is an effect coupled with other actions of the

8   drug or independent, which would be important to

9   consider in clinical care.

10          That notwithstanding, there were a lot of

11  concerns raised about interpretation and the

12  strength of the heart failure data within this

13  study in that it was not designed primarily as a

14  heart failure study.  There is data that one would

15  like to have that aren't there in terms of baseline

16  heart failure data and other modes of assessment of

17  heart failure issues about the definition of heart

18  failure.  And the point was even raised that we may

19  need better metrics for heart failure.  So

20  certainly, in considering future studies, that's

21  something that one has to grapple with as best as

22  one can.

1          I would say that's a summary.  Anything to

2     add?  Dr. Rosenberg?

3          DR. ROSENBERG:  It's just a little side

4     comment.  If you accept that the drug is effective

5     in reducing cardiovascular mortality, you have to

6     consider in which population you'll be able to

7     ethically randomize patients to the drug if you

8     want to study heart failure.

9          DR. SMITH:  FDA, is that enough input from

10    us or do you want more discussion of this?

11         (No response.)

12         DR. SMITH:  So we'll go to the next

13    discussion question, which is to discuss the renal

14    findings in the EMPA-REG OUTCOME study.  Please

15    comment on the potential limitations of these data,

16    if any, and on whether the results of the study

17    establish a benefit of empagliflozin on kidney

18    disease related to diabetes.  Dr. Palevsky?

19         DR. PALEVSKY:  So I don't think that the

20    renal endpoints were rigorously enough collected

21    and adjudicated to really come to strong

22    conclusions.  It's certainly intriguing, the slope

1  of the eGFR change.  But slope of eGFR change, I

2  believe the FDA would not accept as an endpoint.

3         Certainly, the albuminuria seems to be a

4  transient effect.  Stopping the drug, the

5  albuminuria comes back together.  We know that

6  diuretics do that, so I'm not sure that it's

7  telling us anything about structural disease.

8         If this is going to be looked at for a renal

9  endpoint, it's going to have to be looked at with a

10 very rigorous adjudication of whether the change in

11 kidney function is persistent, whether it meets the

12 accepted standards of either a 50 percent decline

13 in -- or reducing the 50 percent increase in serum

14 creatinine or 40 or 50 percent change in eGFR,

15 which was not rigorously done.

16        There will need to be very careful

17 adjudication of AKI versus progression of CKD,

18 which clearly was not done, and understanding of

19 acute versus chronic dialysis, which seemed a bit

20 hazy.

21        I think that there's very intriguing data

22 here, but this is far from the level of data that

1      will establish a specific renal benefit.  And we'd

2      love a drug with a specific renal benefit.

3              DR. SMITH:  Yes, I agree.  And again, just

4      to somewhat reiterate, it's important to separate

5      transient and reversible effects from sustained and

6      longer-term effects.  I know you made that point,

7      but there is a suggestion in the data with the

8      limitations in the data, that there may be some

9      sustained effects, unlike the effect on urine

10     albumin excretion.

11             This is a context again where the other

12     co-variables within the study are critical, as you

13     and I have discussed before.  They are ever more

14     critical because we're looking at microvascular

15     disease where we have a stronger argument for a

16     role of glycemia.  And we know that there was a

17     difference in A1c within the study that one would

18     not want in a study that's evaluating effects on

19     renal complications in diabetes.

20             Similarly, there was an effect on blood

21     pressure, which one would not want in this context.

22     So those issues become, I think, even somewhat

1    greater in terms of limiting the interpretation.

2          Nonetheless, I agree as well that it's an

3    intriguing finding that if it in fact were

4    validated with another study -- and I don't well

5    know that it would be -- that would be a

6    potentially very useful effect of the drug.

7          DR. PALEVSKY:  I would also add, in addition

8    to co-management, we don't know about dosing of RAS

9    blockade, which is the standard of therapy for

10    nephroprotection in these patients, and were there

11    differences.

12          My own personal interest in acute kidney

13    injury -- there is the concern always with an agent

14    that has diuretic effects that there may be an

15    increased risk of subtle AKI, and we have to worry,

16    as we do with RAS blockade, about potential benefit

17    being offset by those risks.  So those are things

18    that really need to be very carefully looked at in

19    order to define the drug as beneficial for kidney

20    disease.

21          DR. SMITH:  Right.  And in fairness to the

22    sponsor, this was not intended to be a study on

1  renal complications and the effects.  It's

2  interesting to see the data, and so these

3  criticisms are not one that are false in this

4  study, they're just things that should be addressed

5  if this were pursued in another study.

6  Dr. De Lemos, were you going to make a comment?

7  No?  Other comments on this?  Yes, Dr. McBryde?

8        DR. MCBRYDE:  I just wanted to reiterate

9  what Paul said, a couple of things that struck me.

10  One was estimated GFR.  The graphs and the

11  statistics look really impressive, but these are

12  estimating equations.

13        They have inherent inaccuracy and

14  imprecision that you can't resolve to 7 mLs per

15  minute, to 1.73 meters squared.  MDRD, even CKD-

16  EPI, you've looking at 20 percent variability with

17  90 percent confidence.  And at an estimated GFR

18  over 70, your error is going to be far greater than

19  what you're resolving in this, and so I think the

20  data is really confusing the way it was expressed.

21        One thing that I was interested in was the

22  albuminuria issue.  What strikes me is it doesn't

1    look like it's really hemodynamic.  There's only

2    about a 4-millimeter systolic blood pressure

3    change.  This is not the SPRINT trial where you got

4    20 millimeters of reduction and you would expect to

5    see a dramatic reduction in albuminuria and it

6    resolved relatively quickly.

7         One of the things that intrigued me about

8    this class of drugs is they are all very highly

9    protein bound.  They are protein bound to albumin,

10   and with nephelometry, it could actually be giving

11   you an erroneous reading, and that would be

12   something I would throw out there.

13        Certainly calcium, some other drugs have

14   been implicated in throwing off turbidimetric and

15   nephelometric measurements.  So thinking long term,

16   you might want to think about something more

17   sensitive, like HPLC or other radioimmunoassays

18   rather than this particular approach.

19        So I am not sure I have any confidence in

20   the data.  It wasn't prespecified, so I don't want

21   to beat anybody up for it.  And as Paul said, I

22   would love to see something that protects the

1    kidneys in this population.

2         DR. SMITH:  So I might summarize that the

3    data themselves, even though presented in a simple

4    way, they may show evidence for benefit in terms of

5    renal outcomes, that there are really major

6    deficiencies in the study design and other aspects

7    of the way the data were collected, and the data

8    themselves that provide no confidence in terms of

9    interpreting these data as a solid demonstration of

10   renal benefit.

11        That clearly would be a very important

12   accomplishment if that were shown in a subsequent

13   study, but it's clear, to the points made by

14   committee members, that really that would need much

15   further study to approach that point.  Okay?

16        So we need to take a break, and when we come

17   back, we'll address the voting questions.  And so

18   we'll take I think about a 10-minute break now, if

19   you would come back here within about 10 minutes.

20        I just again remind committee members that

21   there should be no discussion of the topic or the

22   elements of these considerations among yourselves,

1    other than in the open forum of the committee.

2           (Whereupon, at 3:45 p.m., a recess was

3    taken.)

4           DR. SMITH:  All right.  So we're going to

5    get started again.  I notice in the morning when I

6    say everybody should take their seats, in a couple

7    minutes it gets instantly silent, even though we're

8    not going to start right away.  And about this time

9    of day, nobody listens anymore, keep talking, and I

10   don't blame you for that.  So anyway, here we go

11   again.

12          We're now going to proceed with the voting

13   questions.  We will be using an electronic voting

14   system for this meeting.  Once we begin the vote,

15   the buttons will start flashing on the microphone

16   units, and they'll continue to flash even after

17   you've entered your vote.  Please press the button

18   firmly that corresponds to your vote.  If you're

19   unsure of your vote, or if you wish to change your

20   vote, you may press the button you want until the

21   vote is closed.

22          After everyone has completed their vote, the

1    vote will be locked in.  The vote will then be

2    displayed on the screen.  The DFO will read the

3    vote from the screen into the record.  And next,

4    we'll go around the room and each individual who

5    voted will state their name and their vote into the

6    record.  And at that point, you can also state the

7    reason you voted as you did if you want to.  And

8    we'll continue in the same manner until we've made

9    it around the room for those comments and all the

10    voting questions have been addressed.

11    So if there are no questions or comments

12    concerning the wording or the question, we'll now

13    open this first question for voting.  I guess I'll

14    read it.  Question 6, vote.

15    Based on data in the briefing materials and

16    presentations of today's meeting, do you believe

17    the EMPA-REG OUTCOME study results have fulfilled

18    the recommendations laid out in the 2008 FDA

19    guidance for industry by demonstrating the use of

20    empagliflozin to improve glycemic control would not

21    result in an unacceptable increase in

22    cardiovascular risk?  And if yes, consider your

1    rationale for your vote.  If no, provide your

2    rationale and comment on what additional data would

3    be needed.

4          So any clarification needed before we start

5    the voting?  Okay, so the voting, if we could

6    activate the microphones.

7          (Vote taken.)

8          DR. BONNER:  For the record, 23 yes, zero

9    no, zero abstain.

10          DR. SMITH:  Okay.  So we're going to go

11    around the room.  We'll start with Dr. Schambelan,

12    if you would state your name into the microphone

13    and your vote for the record.  And you may make

14    comment on why you voted yes.

15          Since it's 23/0 yeses, it probably doesn't

16    require a long comment from people.  So if you

17    don't make real long comments, we'll get to the

18    next voting question and have more time to make

19    comments about it.  Okay?  Dr. Schambelan?

20          DR. SCHAMBELAN:  My name is Morrie

21    Schambelan.  I voted yes, and I have no comment.

22          (Laughter.)

1        DR. BUDNITZ:  Dan Budnitz, voted yes.  I'll

2   save my comments for the second question.

3        DR. COOKE:  David Cooke.  I voted yes.  I

4   think it's clear that they met the criteria.

5        DR. NEATON:  Jim Neaton.  I voted yes.  It

6   is very clear they met the criteria.

7        DR. CHO:  Leslie Cho.  I voted yes.  Ditto.

8        DR. FRADKIN:  Judy Fradkin.  Also yes.  Also

9   ditto.

10        DR. ROSENBERG:  I voted yes.  Interesting

11   they made it for the MACE and the MACE-plus despite

12   the limitation for the last component of the

13   MACE-plus.

14        DR. MCBRYDE:  Kevin McBryde.  I voted yes

15   for the same reasons previously cited.

16        DR. EVERETT:  Brendan Everett.  I voted yes.

17   I think they've demonstrated cardiovascular safety.

18        DR. SMITH:  Robert Smith.  I voted yes.  And

19   after I told everybody to not say very much, I was

20   impressed not only at meeting the criteria, but in

21   the various ways of reanalyzing the data addressing

22   questionable groups, various sensitivity analyses.

1    I mean, this effect held up.  So we're not moving

2    through this, in my opinion, quickly because we

3    feel like going quickly, I think it was really very

4    clear viewed from multiple potentially critical

5    directions.

6         DR. THOMAS:  Abraham Thomas.  I voted yes.

7    And I really agree with Dr. Smith that, of all the

8    things we discussed this afternoon and this

9    morning, this is the clearest.

10        DR. KONSTAM:  Marv Konstam.  Yes.

11        DR. LI-NG:  Melissa Li-Ng.  I voted yes.

12   And I concur with all the previous comments.

13        DR. GOOD:  David Good, yes.

14        DR. DE LEMOS:  James De Lemos, yes.

15        MS. HALLARE:  Diana Hallare, yes.

16        DR. PALEVSKY:  Paul Palevsky.  Yes.  No

17   further comments beyond what's been made.

18        DR. WILSON:  Peter Wilson, yes.

19        DR. HECKBERT:  Susan Heckbert, yes.  The

20   data were very convincing regarding safety.

21        DR. YANOVSKI:  Susan Yanovski, yes.

22        MR. LUMLEY:  Dan Lumley, patient rep.  Yes.

1          DR. HIATT:  William Hiatt, yes.  And it was

2     convincing.

3          DR. PROSCHAN:  Michael Proschan, yes.

4     Because, duh.

5          (Laughter.)

6          DR. SMITH:  You realize that's in the

7     federal record?

8          (Laughter.)

9          DR. PROSCHAN:  I've done a lot worse than

10    that in the federal record.  No problem.

11         (Laughter.)

12         DR. SMITH:  So I think we'll go to the

13    second voting question.  So for this voting

14    question, I will read.

15         Based on data in the briefing materials and

16    presentation at today's meeting, do you believe the

17    EMPA-REG OUTCOME study results provide substantial

18    evidence to establish that empagliflozin reduces

19    cardiovascular mortality in the population studied?

20    If yes, please provide the rationale for your vote.

21    If no, please provide the rationale for your vote

22    and comment on what additional data would be

1    needed.

2          Any questions, clarification questions

3    regarding the -- yes, Dr. Hiatt?

4          DR. HIATT:  I would just like to clarify

5    with the FDA on this question.  Vis-a-vis a meeting

6    we had a year ago, if we vote yes, and this goes in

7    the label, and no other drug of this class

8    substantiates that, you're stuck with that.  Right?

9    You can't withdraw that unless there's a new safety

10   concern that might change how you feel.

11         But I just want to understand, if we put

12   this in, and based on this single trial, then the

13   sponsor gets that claim regardless of whatever

14   happens after that.  Is that correct?

15         DR. GUETTIER:  It's very hard to take a

16   claim out once it's in the label because the other

17   trials that are negative may be negative for some

18   very good reasons.  So I think what we're asking

19   you to opine on today is with the data that you've

20   heard today, whether or not you think this is

21   believable enough to be included as a claim in the

22   label.

1          DR. SMITH:  So I'd like to ask for a little

2   clarification on that because I can read this

3   question one way, which doesn't mention a claim.

4   Or I could read this question in a way that would

5   say, do I think the FDA ought to put this claim in

6   effect.  And so I would like to clarify what you're

7   asking us.

8          DR. GUETTIER:  So this question was really

9   was meant to actually get at the issue of a claim.

10  It talks about substantial evidence to establish

11  that empagliflozin reduces cardiovascular

12  mortality.  And as you heard this morning,

13  substantial evidence is the evidence necessary to

14  form the basis of a new claim.

15         The new claim the sponsor is seeking, as of

16  today, is a cardiovascular mortality benefit.  It

17  wasn't the initial claim that they sought, but this

18  is the new claim.  So really what this question is

19  asking you is whether or not the evidence that is

20  provided by this trial is substantial evidence and

21  warrants inclusion in the product label.

22         DR. KONSTAM:  Can I follow that for a

1   second?  Oops, I voted.  I might not have meant

2   that vote.  So, if you decide not to give it the

3   claim, is it likely, nevertheless, that the data

4   would appear in the label?

5           DR. GUETTIER:  Basically without a claim,

6   it's unlikely that the data would appear in the

7   label.  The data in the label describes in

8   general -- so section 14 of the label generally

9   describes the trial that supports the indication.

10  And so if there is no indication, there is no

11  claim.

12          That being said, this is now a safety trial

13  and we would likely put at least the safety

14  component of the trial.  How we would do that, we

15  haven't really gotten to.

16          DR. SCHAMBELAN:  Could I ask a question as

17  well?  So since the claim here is for

18  cardiovascular mortality and not for a MACE

19  outcome, are we in a position that we can, if we

20  have concerns about the MACE outcome, that we can

21  ignore that in answering this question?

22          DR. GUETTIER:  I think that your vote should

1   be informed by the discussion at this afternoon's

2   session, and I think you've heard some thoughtful

3   comments by other members of the committee

4   regarding how to think about the cardiovascular

5   mortality claim.  And so we think that the

6   discussion that occurred this afternoon should at

7   least should have informed how you vote about this.

8       Again, this is asking about the

9   cardiovascular mortality claim.  You've heard both

10  from the FDA presentation, from comments that were

11  made by some of the members that in order for you

12  to look at this particular component of the

13  composite, you have to be convinced that you've won

14  on the primary endpoint, et cetera, et cetera.  So

15  those are some of the things that you should be

16  thinking about as you vote.

17      DR. SMITH:  Further questions, clarifying

18  questions.

19      DR. KONSTAM:  You've got two over there.

20      DR. SMITH:  Sorry.  Dr. Good?

21      (No response.)

22      DR. SMITH:  Dr. Li-Ng?

1          DR. LI-NG:  Sorry, a question for the FDA.

2     So how would you interpret -- so the question that

3     you're posing is, is there substantial evidence to

4     establish that empagliflozin reduces cardiovascular

5     mortality in order to for it to have this

6     indication.  So, because there are other

7     ramifications of adding this to the label for this

8     particular class of medications, how would you

9     interpret then a yes versus a no.  Or maybe that's

10    not an appropriate question at this point.

11         DR. GUETTIER:  I think you know what we've

12    said early today is that, as important as the vote

13    is in terms of yes or no, is the rationale for why

14    you voted.  And so you can basically explain why

15    you voted the way you did.  And based on your

16    rationale, we do look at the record and the yes and

17    no is not always black and white.

18         DR. SMITH:  Yes, Dr. Good?

19         DR. GOOD:  So the implication is that we

20    feel that the recommendation would stand on this

21    single trial and would not require a second trial

22    really.  That's kind of the implication of this.

1          DR. SMITH:  I would interpret it that way

2     because it's based on the data in the briefing

3     materials as written in this question, yes.  Other

4     clarifying questions?  Dr. Rosenberg?

5          DR. ROSENBERG:  Yes.  It's not a

6     clarification but just confirmation that from the

7     FDA they can always disagree with the

8     recommendation.  Right?

9          (Laughter.)

10         DR. SMITH:  So I think we're ready to go

11    ahead with the vote.

12         (Vote taken.)

13         DR. BONNER:  For the record, vote question

14    number 7, 12 yes, 11 no, and zero abstain.

15         DR. SMITH:  So again, we'll go around the

16    room.  We're going to start this time on the other

17    side of the room.  Dr. Proschan, you're first, if

18    you would state your name into the microphone for

19    the record, your vote, and any comments you'd like

20    to make on the basis for your vote.

21         DR. PROSCHAN:  I'm Michael Proschan.  I

22    voted yes.  I think the evidence was pretty robust.

1    I feel pretty confident that there's some benefit

2    on cardiovascular mortality.  I think it's likely

3    that that 38 percent is an overstatement that's

4    probably biased.  But I think, even if it's 20

5    percent, you know that's still very good.

6         I would not have voted yes on the original

7    claim they made, but I think, because of the many

8    events, because of the sensitivity analyses, I feel

9    pretty confident that there is some benefit on

10   cardiovascular mortality.

11        DR. HIATT:  William Hiatt.  I voted yes.  In

12   reviewing the data before this meeting, I was not

13   convinced.  And in particular, I was concerned

14   about the idea that the MACE endpoint barely made

15   it in.  But that in and of itself would probably

16   not have been a convincing result.

17        The thing that swayed my thinking about this

18   particular question was that cardiovascular

19   mortality withstood all the sensitivity analyses,

20   including the worst-case missing data analysis of

21   assuming a complete reversal of events between drug

22   and placebo.  So with that kind of evidence, it's

1    hard to explain it away.

2         I don't understand the mechanism, but it

3    seems that that is a highly clinically important

4    result, and I would hate to sort of deny a claim

5    based on the unique way this trial was run and how

6    this finding evolved, because I believe at the end

7    of the day, I think the result is true.

8         MR. LUMLEY:  I'm Dan Lumley.  I voted yes.

9    As I indicated before, I'm the patient rep.  I've

10   had type 2 diabetes for 20 years.  My disease is

11   under control largely because of drugs, diet,

12   exercise, a Kansas City caring doctor, and recently

13   the Kansas City Royals winning last year's World

14   Series.  It made me feel a hell of a lot better.

15        But that's not the reason I voted yes.  The

16   reason I voted yes is, from what I heard today, I

17   think it works, and it's safe.

18        DR. YANOVSKI:  Susan Yanovski, and I also

19   voted yes.  I was impressed with the magnitude of

20   the reduction of CVD and all-cause mortality, which

21   I think really represents the hardest of hard

22   outcomes.  We were shown statistically strong

1    evidence of important clinical benefit in a large

2    multi-center study, which was one of the FDA

3    criteria for accepting data from one study.

4         I do understand the uncertainty that's

5    imposed by having a fairly large proportion of

6    non-assessable CV deaths, but I was reassured by

7    the sensitivity analyses, particularly those

8    showing a significant CV death risk reduction, even

9    after you excluded those deaths.

10        DR. HECKBERT:  This is Susan Heckbert, and I

11   voted no.  I agree particularly with the points

12   that Dr. Hiatt brought up that this trial does

13   provide evidence of reduction in cardiovascular

14   mortality.  I think it's intriguing and it would

15   really be great if this is, as it appears to be,

16   correct.

17        But I think the question we're asked to vote

18   on today was whether the available data is adequate

19   to support an additional indication in patients

20   with established CVD to reduce the risk of

21   cardiovascular death.

22        I believe that given the issues with the

1    non-assessable causes of mortality, the fact that

2    cardiovascular mortality was not a primary

3    endpoint, and the issues of multiple testing that

4    we've discussed today, and also the fact that the

5    FDA usually requires two well-designed and

6    conducted trials to add this type of an indication,

7    taking all those things together, my opinion is

8    that although these data are intriguing and

9    promising, a second study is needed before this

10    indication would be added.

11    DR. WILSON:  Peter Wilson.  I voted no.

12    This is the first compound in this class going for

13    this indication.  And I think we should have a

14    higher bar for the quality of the evidence and the

15    importance of the findings, they really be

16    substantiated.

17    I think it's very hard to go from safety to

18    superiority in one study.  I have difficulty with a

19    trial that has nine modifications as it went

20    through the path to eventual conclusion and

21    readjustment of some of the key issues that may

22    have been intervening issues, and especially

1 concerning because the blood pressure effect, and

2 potentially the heart failure effect, may be the

3 most important pathways.  And the heart failure

4 one, we'd all like to see more information and

5 better information.

6  I am concerned that if approved, the

7 medication might be overused in younger patients at

8 fairly low risk of heart failure and extremely low

9 risk of cardiovascular death.  So I think a second

10 study that would really confirm these and firm up

11 who are the candidates would be important.

12  Then finally, what trial would be the next

13 trial?  So I think as people with heart failure or

14 at high risk for heart failure, with a variety of

15 modern approaches and assessments.

16  DR. PALEVSKY:  Paul Palevsky, and I voted

17 no.  I can see that the results on mortality are

18 very intriguing.  I think that there are a number

19 of issues that have already been discussed about

20 concerns regarding the unable to be classified

21 cardiovascular deaths.

22  I'm concerned about the fact that we really

1    don't know what the mechanism is, and we don't know

2    whether there may be other aspects of interventions

3    in these patients that may have been contributing

4    to the apparent benefit from the drug rather than

5    it necessarily being a true drug.

6         This is a drug that's on the market.

7    Prescribers will have access to the published

8    literature about the drug.  But I think that before

9    it's labeled, we have to have confirmatory

10   evidence.

11        MS. HALLARE:  Diana Hallare.  I voted no.

12   This is because of the missing data, the unblinding

13   of certain individuals, the uninterpreted deaths,

14   silent MI controversy.  And I would like to see

15   more as additional data, a more diverse population

16   in this study, including ethnicity, those with or

17   without heart failure, those at risk for kidney

18   disease, for instance.  And I know currently that

19   there is a clinical trial going on for a particular

20   subgroup, and I think that is commendable.  And I

21   believe that a second trial would provide more

22   clarity.

1        DR. DE LEMOS:  I'm James De Lemos.  I voted

2    yes.  I struggled as well with the classification

3    of the cardiovascular death events and the likely

4    misclassification of the events and acknowledge as

5    well that the effect size is likely dramatically

6    overestimated and probably wouldn't replicate to

7    this degree.

8        But the robustness of the finding, the large

9    number of endpoint events, and then most

10   importantly, the fact that it's buttressed by a

11   reduction in all-cause mortality, the ultimate

12   endpoint to me, drove a narrow decision in favor of

13   approval, for recommendation for approval.

14       DR. GOOD:  David Good.  I also came down

15   narrowly on the side of yes, for pretty much the

16   same reasons that already been elucidated by my

17   colleagues in the room.

18       I felt that the cardiovascular mortality was

19   always reasonable robust.  If I had to vote only on

20   the primary outcome measure of 3-point MACE, I

21   would have voted no.  I'm also concerned about the

22   mechanism, but that didn't dissuade me from voting

1    yes after considering this quite carefully.

2         DR. LI-NG:  Melissa Li-Ng.  I voted no for

3    similar reasons that have already been stated.  For

4    me, as an endocrinologist, the lack of a mechanism

5    does bother me.  I was thinking that clinically.  I

6    practice in a region where SGLT2 inhibitors were

7    approved before the U.S. FDA approved them, so

8    they've been in use for about three or four years

9    already.  And for me to tell a patient that now

10   this has been shown to decrease your risk of dying

11   from all causes based on one study, despite the

12   robust evidence, again, it's very hard for me to be

13   able to say that to a patient without a second

14   study to confirm these findings.

15        DR. KONSTAM:  Marv Konstam.  I voted yes.

16   First of all, I want to say to my colleagues on the

17   FDA, good luck in figuring out what to do.

18        (Laughter.)

19        DR. KONSTAM:  I think that the vote actually

20   is, as it turned out, is very representative of

21   what's been going on in my mind all day long, of

22   going back and forth about what the right thing to

1  do here is.  And I will say that every member to my

2  right that's voted no, I agree with what they said.

3  Okay?

4        (Laughter.)

5        DR. KONSTAM:  So I agree with everybody.

6        (Laughter.)

7        DR. KONSTAM:  I think that -- so it's tough,

8  because we have a component of an endpoint, which

9  is a secondary endpoint, that hits its p-value

10  marginally.  And so for that reason, despite, I

11  think, Dr. Pocock's really excellent presentation,

12  I just don't know what that p-value really is.  And

13  I think the comment about multiplicity has been

14  stated a number of times, and so I have trouble

15  getting there in any kind of rigorous way

16        So why did I vote yes?  I hope and I think I

17  alluded to some of it in my comments, it's really

18  pulling it together with three pieces of

19  information.

20        One is that the p-value, nominal as it is,

21  is extremely small.  Two is that -- and this hasn't

22  been discussed quite enough.  I think in a way

1   there are two trials in here, with two different

2   doses, and each of those populations -- those two

3   populations with the two doses behave pretty much

4   exactly the same.

5         So that influenced me.  And I was influenced

6   by the number of events.  I think 300 and whatever

7   we said, over 300 events is a substantive finding,

8   and in my mind weighs a little.

9         I appreciate Bob Temple bringing up the LIFE

10   trial because I think that's kind of a precedent

11   for what you're dealing with here because you have

12   a primary endpoint that's there that's positive,

13   but with a soft p-value and without another trial,

14   and then you went ahead and approved a component of

15   the primary endpoint -- so there's some analogy

16   here at least.  Maybe you had no idea what you were

17   doing, but you set a precedent.

18         (Laughter.)

19         DR. KONSTAM:  So anyway, that was my

20   rationale, and I wound up voting yes.

21         DR. THOMAS:  Abraham Thomas.  I voted yes.

22   I think the data was very convincing.  The p-value

for the composite was the one we're all having

doubts about. However, the mortality is very

convincing. And fortunately, the all-cause

mortality is consistent, so this isn't a case where

in some previous trials, we got an improvement in

cardiovascular mortality and all-cause mortality

goes the wrong way because people are driving their

tractors into fjords and random events like that.

I think what's important, though, is -- and

what I was wrestling with is do you require a

second trial or not. And I voted yes thinking that

you probably don't, but there are a lot of

unanswered questions, the mechanism, heart failure,

things that could be studied in additional trials.

And I do echo the point of if you really are a

purist, really in some respects this is a very

enriched population, appropriately so for a

cardiovascular event trial.

How does this translate to the new diabetic?

We really don't have very good tools of changing

mortality in newly diagnosed diabetics. Several

trials have looked at that and saw no difference in

terms of the treatment arm or the placebo arm.

Does this agent add some promise to the newly

diagnosed diabetic?  And is this an agent that you

would add even if glucose control is reasonably

under good control?

I mean, these are questions that we'll have

to ask.  Is this something that's going to be not

just a diabetes drug, but an add-on for

cardiovascular safety in diabetics?  So I think

there's still a lot of unanswered questions that

would require another trial, but not necessarily

for the indication.

It's in the literature, so people know about

this, but we know people don't act on knowledge

even when they're from very well-done large trials.

There's inertia to doing this.  However, patients

can only get medications that their insurance

covers.

I have a feeling if there is an indication,

that might drive the coverage of some of these

medications for the insurers, the pharmacy benefit

managers.  And if there really is a mortality

1  benefit like this trial showed, that would be an

2  important thing for our patients, and patients do

3  care if they die or not.

4      DR. SMITH:  I'm Robert Smith.  I voted no.

5  It was a very difficult decision.  So again, it was

6  for me a narrow split, a very narrow cut between

7  yes and no.  Focusing on the mortality data of this

8  trial, I feel that they are very robust.  And so as

9  one trial goes, this is a convincing set of data.

10     But then as I think about not just what do I

11 think about the outcome of this trial, but how

12 confident would I be that a second trial would

13 reproduce these data, I feel enough uncertainty

14 that that's the basis for my no vote.

15     I think the issues behind that were very

16 well summarized in combination by Drs. Wilson and

17 Palevsky in terms of issues related to the study

18 population, and things about the study itself that

19 we may not appreciate from a single study as

20 important variables, as well as a number of aspects

21 of how the study itself was conducted, which are

22 individual to a study.

So I agree it's a very difficult problem that now goes to the FDA, but I was not comfortable enough that these robust data would be reproduced by subsequent experience to give a yes vote.

DR. EVERETT:  Brendan Everett, and I voted yes.  I think there was some concern, probably most eloquently expressed by Marv, about the robustness of the win on the primary endpoint, because once you demonstrate that, then you can get through the door and start looking at the components of the primary endpoint.

But I think once you're through that door, which I felt okay that we did get through the door, the effect on cardiovascular mortality is clear and substantial, and as others have mentioned, survives multiple sensitivity analyses.

The thing that really drove this vote for me was the number of events, cardiovascular deaths, and the size of the p-value, and the importance of that particular endpoint.  I don't think I would have voted the same way if the endpoint were myocardial infarction, for example.

1          That said, I struggled, as many others have,

2     in the great tradition of a yes vote meaning no,

3     and a no vote meaning yes for the FDA.  I think

4     that, like Dr. Smith mentioned, I think this is one

5     trial.  It's not two trials; it's one trial.  And

6     that makes me hesitate about the fact that these

7     results really have not been replicated, whether by

8     this agent or by another agent in this class.

9          As the FDA is turning these comments over,

10    over the course of the next couple of months, I

11    would not object to waiting to give the label until

12    there are a second or third endpoint trial that

13    includes cardiovascular death as one of its key

14    components.

15         I suspect -- I don't know this for

16    sure -- that the sponsor is planning trials in

17    other select populations that might have a

18    significant benefit from this drug.  I certainly

19    hope so because one of the reasons I voted yes is

20    because this is enormously promising, and I think

21    potentially offers a benefit to a huge number of

22    patients who have not, as of yet, had any agent for

1    managing glucose that reduces their cardiovascular

2    mortality.

3          DR. MCBRYDE:  Kevin McBryde.  I voted no.

4    I'd reiterate a lot of the same sentiments that

5    have been discussed earlier.  I think what struck

6    me -- I think the MACE 3 endpoint was pretty clear

7    it did not meet the statistical significance that

8    was predefined.

9          The cardiovascular mortality bothers me a

10    little bit.  This was a population of 76 percent at

11    baseline who had evidence of coronary artery

12    disease and yet myocardial infarction didn't pan

13    out as cause of cardiovascular death.  And that

14    just set off a little red flag in my mind.  Ten

15    percent of the patients were diagnosed with having

16    heart failure at baseline, and yet hospitalizations

17    were much greater for heart failure.

18          There were some inconsistencies in terms of

19    hazard ratios across regions.  Looking at a

20    population -- and again this is only -- I'm

21    speaking purely from the U.S. perspective where 1

22    in 6 Americans with diabetes are black or

1  African-American and 5 percent of the study

2  population represent them -- and the data suggested

3  in that small body that there might be an increased

4  risk for that population.

5       I just think that it was a little bit too

6  much to overlook under the criteria that FDA gave

7  for acceptance of a single trial versus requesting

8  a second.  And I think I would feel a little bit

9  better for the U.S. population specifically with a

10  second trial that could support these findings.

11       DR. ROSENBERG:  Yves Rosenberg.  I voted no,

12  but also, as many others have mentioned, it was a

13  very difficult decision.  Maybe the FDA should have

14  a third category that's maybe.

15       (Laughter.)

16       DR. ROSENBERG:  Second, I want to thank Dr.

17  Konstam.  I'm glad I helped Dr. Konstam reach a

18  decision that's opposite to me by having raised

19  issue of naming the LIFE study that Dr. Temple

20  reported also got to an opposite decision.

21       Again, the same reasoning that's been

22  mentioned already; it's a secondary endpoint among

1    many.  And although the results are probably true,

2    p-value is not what's really important.  It's the

3    confidence interval.  And what am I going to say to

4    a patient?  Yes, it will probably reduce your

5    mortality, but maybe it's a little bit and maybe

6    it's a lot.  I think your patients deserve better.

7    They deserve more evidence, and that's why a second

8    trial is required.

9         Again, among the other reasons that were

10   mentioned, it's the first component in class and if

11   we say if it's approved it's probably the end of

12   the story in this class, and really, we need many

13   evidence.

14        Also, yes, it may not be reimbursed for all

15   its drugs that's still already on the market, but

16   it's available if people really think it will

17   benefit them.  But we really need to make sure of

18   the magnitude of benefit, on which patients it

19   really works.  The issue of African-American is

20   very important in this country, so we need to

21   answer that question.

22        Yes, probably the sponsor is not very happy

1   now, but already probably they're doing studies

2   there, so hopefully it's not too much of an added

3   cost for them.  And maybe they can talk to the new

4   leadership of the FDA or talk about ways they can

5   do their study a little more efficiently than have

6   been so far.  I think that's all.

7        DR. FRADKIN:  I'm Judy Fradkin.  I voted no.

8   I also really struggled because my answer to the

9   question as to whether there's substantial evidence

10  would have been yes.  I just don't think it's

11  absolutely proven to the extent that it should get

12  a label.

13       I was very impressed by the number of

14  events, the magnitude of the reduction, the

15  sustained effect over time, the sensitivity

16  analyses.  I thought all of that was really

17  compelling.

18       What I just couldn't get past was sort of my

19  longstanding belief that a positive outcome to a

20  secondary outcome is hypothesis generating.  And I

21  wasn't convinced that the primary outcome was

22  clearly positive given some of the methodologic

1    issues in the study.

2         That said, even if some of the other agents

3    in this class didn't show a cardiovascular

4    mortality benefit, I wouldn't say that that

5    excludes this one showing it.  I think these drugs

6    differ in terms of their selectivity.  And I

7    thought that there was a lot of really promising

8    evidence for this.  And I am reassured by the fact

9    that doctors will see this data and make their own

10   decisions, but I did feel that we needed a second

11   study before there's a label.

12        DR. CHO:  My name is Leslie Cho.  I voted

13   yes.  I voted yes for many reasons.  One is that

14   since 2008, the FDA guidance has really led the way

15   from all these diabetic medications to undergo

16   these cardiovascular trials that we've seen time

17   and time again.  They've been negative.  We've seen

18   that for GLP-1.  I mean, we've seen that for DPP-4.

19   We've seen it in 16,000-patient trials, such as

20   SAVOR, where there was absolutely no cardiovascular

21   death benefit on the active arm.

22        So for this trial to be so positive in terms

1    of overwhelming cardiovascular death numbers, and

2    even with the sensitivity analysis to be positive,

3    that was very convincing for me.  And I think as a

4    cardiologist, it's interesting to note that all the

5    cardiologists on the panel voted yes, which is kind

6    of interesting as well.  It's just a side note

7    there.

8         I don't think we have to -- we've

9    traditionally thought about cardiovascular endpoint

10   as athero endpoints, but perhaps it's now time to

11   move away from athero endpoints to something

12   different.  And yes, it's a mechanism we don't

13   know, but it's still the number of deaths, the

14   actual bodies on the ground.  It's pretty

15   convincing.

16        DR. NEATON:  Jim Neaton.  I voted yes.  An

17   extreme difference and a very clinically relevant

18   outcome, with a relatively narrow confidence

19   interval based on the large number of deaths.  An

20   endpoint, which is very easily ascertainable, less

21   than 1 percent, were missing.  The findings held up

22   to a worst case analysis very easily.

1          In this population, one would expect a large

2     number of cardiovascular events.  So I thought the

3     two analyses, one where you excluded the

4     non-assessable events, and then the second where

5     you just looked at all-cause mortality, both kind

6     of were supportive and very convincing.

7          I thought the discussion that we had around

8     some of the non-fatal outcomes, maybe the lesson

9     from this is that we should be doing more trials

10    with cardiovascular all-cause mortality outcomes

11    that are easily ascertainable where the results are

12    very clear-cut when you get them.

13         DR. COOKE:  David Cooke.  I voted no.  And

14    for me, it also was a difficult decision.  And I

15    did go back and forth throughout the day in terms

16    of what I thought made sense.

17         But it came down to this question of whether

18    this trial should stand alone as the evidence for

19    benefit on cardiovascular mortality for this

20    medication.  And I really think the data to support

21    a single trial as evidence of efficacy needs to be

22    very high.  And I think just this uncertainty to me

1    almost defines the fact that that really says we

2    need another trial to clarify this.

3          Yes, the data on cardiovascular mortality in

4    this trial is very suggestive of a benefit, but it

5    is just a single trial.  And kind of folded into

6    that is this issue of mechanism.  And I don't feel

7    that we absolutely have to understand a mechanism

8    to accept a benefit, but we do have to have at

9    least an understanding in some ways of who is going

10   to benefit from a medication like this.

11         The most obvious question with this

12   medication is, what is this impact on heart

13   failure.  I think we definitely don't have our

14   hands around that because the study wasn't designed

15   to investigate that sufficiently.  So I think we

16   need to understand that.

17         Or if that's not the answer to how this is

18   benefiting patients, then understand how we can use

19   this to benefit patients if it's supported by a

20   second trial.  But I do feel that use of a

21   secondary outcome as the final answer to an

22   efficacy trial is risky.

1          DR. BUDNITZ:  Dan Budnitz.  I voted no.

2     Like David, I had some concerns about this being

3     the single trial in the end.  I think there

4     probably is likely a mortality benefit, but had

5     enough concerns that I wanted to go over those four

6     characteristics that were outlined at the beginning

7     of the day about when FDA has relied on a single

8     trial.  Included excellent study design, highly

9     reliable, statistically strong, and evidence of

10     important clinical benefit.

11          Just going through those, I think it was

12     excellent design as a safety study, but I think we

13     heard about -- there's enough concerns that this

14     might not be the ideal design for looking at CV

15     death as a primary endpoint.  Is it highly

16     reliable?  We heard about issues of multiplicity,

17     the other CV death that was not further described,

18     the numerous changes to protocol that might

19     question the reliability.

20          The question of statistically strong, I

21     think on the surface obviously it's a very small

22     p-value.  But digging into issues of multiplicity

1    and the methodologic, the statistical methodology

2    of looking at this secondary endpoint after there

3    was a barely statistical MACE endpoint, raises

4    concerns.

5         Finally, is this an important clinical

6    benefit?  Of course, cardiovascular mortality is,

7    but for me the question was, is it generalizable to

8    my patients here in the U.S., because that's what

9    the indication is for.  And I just don't know

10   because didn't know enough about the patients'

11   baseline drugs, what usual care entailed over the

12   course of the study.  So I would very much look

13   forward to a second study with, if not all in the

14   U.S., with a strong U.S. component.

15        DR. SCHAMBELAN:  I'm Morrie Schambelan.  I

16   voted yes.  I think Dr. Neaton expressed most of

17   the thoughts that I had about this.  I did go back

18   and forth during the day.  I wish the FDA good luck

19   in trying to decide what they're going to do with

20   our input. concerned, though, that we make sure

21   that the population who

22        I am is treated with this drug, if this

1    indication is approved, are the people that were

2    studied in this trial.  And I don't think we're

3    ready to give it to the 19-year-old diabetic, the

4    concerns that Peter Wilson raised.

5         So I was very, very close to wanting that

6    second trial, but I'm so impressed with this impact

7    one, the most important outcome, and the fact that

8    all-cause mortality was the same, I would hate to

9    see this not available to people in the attempt to

10    try to keep them alive.

11         DR. SMITH:  Dr. Kewalramani, as the industry

12    representative, you don't vote, but do you have any

13    comments you'd like to make?

14         DR. KEWALRAMANI:  Thank you.  I have no

15    additional comments.

16         DR. SMITH:  How about the FDA, any further

17    comments from you?  Any closing remarks you'd like

18    to make?

19         DR. GUETTIER:  I think you've just made our

20    job easier.  Thank you.

21         (Laughter.)

22         DR. GUETTIER:  I'd like to extend my thanks

1    to the DMEP review team for their hard work in

2    preparing for this; for our colleagues from the

3    Division of Cardiorenal Products for their help in

4    preparing for this advisory committee meeting; for

5    the applicant in the weeks leading up to this AC.

6    We did issue a lot of information requests to get

7    to the bottom of some of the issues that were

8    raised in the review, and they were very timely in

9    their responses.

10           Then for the members of the advisory

11   committee for all your input today, I think it's

12   helpful to us and we'll take everything that you've

13   said today into consideration.  So thank you.

14                       **Adjournment**

15           DR. SMITH:  I, too, would like to thank the

16   committee members for your very thoughtful comments

17   and discussion today.  This obviously was a

18   difficult discussion and so special thanks also to

19   the sponsor and to the FDA for all the data you

20   provided to us and all the assistance in our

21   questions.  We very much appreciate it and it's

22   really helped with the process, so we appreciate

1    that.

2         So with that, this meeting is adjourned.

3    The committee members, please remember to drop off

4    your name tags at the desk so they can be recycled.

5    And thanks everyone for participating, including

6    the open public hearing speakers.  We appreciate

7    your input.

8         (Whereupon, at 4:43 p.m., the meeting was

9    adjourned.)

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